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EXPERIMENTAL STUDIES ON HEADACHE

FURTHER ANALYSIS OF HISTAMINE HEADACHE AND ITS PAIN PATHWAYS

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The blood vessels of the head are an important site of origin of nerve impulses interpreted as headache.[1] The purpose of this investigation was to obtain further information concerning the contribution to pain made by the cranial arteries in headache and concerning the nerve pathways which conduct these impulses.

Anatomic and experimental studies have aided in the clarification of the innervation of intracranial structures. Studies on man have shown that all arteries of the scalp are sensitive to pain, as are also the arteries of the dura, except the smaller terminal branches.[2] The more proximal portions (1 to 5 cm.) of the middle, anterior and posterior cerebral and the internal carotid arteries are sensitive to pain, as are the vertebral and basilar arteries and the proximal portions of their branches.[3] It has been shown in cats that the larger cerebral vessels, especially those near the base of the brain, give rise on stimulation to afferent nerve impulses.[4]

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1. Wolff, H. G.: Headache and Cranial Arteries, Tr. A. Am. Physicians **53**:193, 1938.

2. Ray, B. S., and Wolff, H. G.: Experimental Studies on Headache: Pain-Sensitive Structures of the Head and Their Significance, Arch. Surg., to be published.

3. (*a*) Fay, T.: Certain Fundamental Cerebral Signs and Symptoms and Their Response to Dehydration. Arch. Neurol. & Psychiat. **26**:452 (Aug.) 1931. (*b*) Ray and Wolff.[2]

4. Levine, M., and Wolff, H. G.: Cerebral Circulation: Afferent Impulses from the Blood Vessels of the Pia, Arch. Neurol. & Psychiat. **28**:140 (July) 1932.

The middle meningeal artery receives fibers from the second and the third division of the fifth cranial nerve and also, though less constantly, from fine unnamed branches of the first division.[5] The posterior meningeal artery is supplied by the recurrent meningeal branch of the vagus and by fine branches of the twelfth nerve. The anterior meningeal artery appears to derive its nerve supply from the first division of the fifth cranial nerve.[6]

The course of afferent pathways from the pial and the cerebral blood vessels has not been established. Nerve fibers connecting directly with the brain stem or the spinal cord, as well as with various cranial and spinal nerve roots,[7] have been observed to reach these vessels and their branches.

Experiments with nerve degeneration indicate that afferent fibers from the carotid plexus may go to the geniculate ganglion of the seventh cranial nerve and reach the brain through the nervus intermedius.[8] They may also be derived from other cranial nerves, including the fifth.

The studies mentioned, though they point out which structures are sensitive to pain and indicate the distribution of nerves, give only indirect information regarding the pathways that mediate the impulses of headache. To shed light on the problem of pain pathways it seemed important to employ a known pathophysiologic mechanism for the production of headache and to analyze the pathways in terms of this mechanism. For this purpose headaches were induced in subjects by the intravenous injection of histamine.

Analysis of histamine headache [9] indicates that the mechanism of the headache is the dilatation and stretch of pain-sensitive cranial arteries. The dramatic cerebral vasodilatation that follows injection of histamine, as seen through skull windows in cats, suggests that the cerebral arteries are probably important contributors to histamine headache.[10] That relief of histamine headache may be brought about by increasing intracranial

5. Penfield, W., and McNaughton, F.: Dural Headache and Innervation of the Dura Mater, Tr. Am. Neurol. A. **64**:106, 1938.

6. McNaughton, F.: Innervation of the Intracranial Blood Vessels and Dural Sinuses, A. Research Nerv. & Ment. Dis., Proc. (1937) **18**:178, 1939.

7. Clark, S. L.: Innervation of the Choroid Plexuses and Blood Vessels Within the Central Nervous System, J. Comp. Neurol. **61**:21, 1934.

8. Chorobski, J., and Penfield, W.: Cerebral Vasodilator Nerves and Their Pathway from the Medulla Oblongata, with Observations on the Pial and Intracerebral Vascular Plexus, Arch. Neurol. & Psychiat. **28**:1257 (Dec.) 1932.

9. (*a*) Pickering, G. W., and Hess, W.: Observations on the Mechanism of Headache Produced by Histamine, Clin. Sc. **1**:77, 1933. (*b*) Clark, D.; Hough, H. G., and Wolff, H. G.: Experimental Studies on Headache: Observations on Histamine Headache, A. Research Nerv. & Ment. Dis., Proc. (1934) **15**:417, 1935.

10. Wolff, H. G.: The Cerebral Circulation, Physiol. Rev. **16**:545, 1936.

pressure, as ascertained in other investigations,[9] affords further evidence that intracranial rather than extracranial arteries give rise to the painful impulses of headache. Pickering and Hess [9a] suggested that the dural arteries are primarily responsible. More recent studies by Northfield [11] have indicated that the cerebral arteries are the main sources of histamine headache. Before pursuing the problem of nerve pathways further, therefore, it was desirable to obtain additional data on the cranial structures concerned in the production of histamine headache. The first series of experiments had this purpose.

SERIES I

SUPERFICIAL TISSUES OF THE SCALP

Simons,[12] working in the same laboratory as we, blocked all afferent nerves from the scalp on one side, from the midfrontal to the postparietal region, with a 1 per cent solution of procaine. This was done by infiltrating the tissues with procaine hydrochloride in a line extending from the middle of the forehead to the ear and over it. The injection was superficial, presumably including little of the tissue containing the temporal, frontal or supraorbital artery. There resulted analgesia over the entire forehead and temple, extending to the vertex. This procedure was performed on 15 patients.

EXPERIMENT 1.—Four subjects who were given injections of procaine hydrochloride on one side received intravenous injections of histamine phosphate, 0.1 mg., immediately after the local analgesia had been produced. The subsequent histamine headache was severe, generalized and of equal intensity and distribution on the two sides of the head.

EXPERIMENT 2.—In 11 subjects subsequent injection of air into the subarachnoid space of the lumbar region for encephalographic study was accompanied by headache, which was of the same distribution and intensity on the two sides of the head. The unilateral analgesia had no appreciable influence on the headache of the corresponding side.

These observations indicate that the headache resulting from histamine and from injection of air into the subarachnoid space does not depend on the integrity of superficial sensation. The suggestion of Weiss and Davis [13] that visceral pain is dependent on the presence of superficial or cutaneous impulses is therefore untenable for the headache described here.

TEMPORAL, FRONTAL AND SUPRAORBITAL ARTERIES

Effect of a Tight Head Bandage.—Pickering and Hess reported that in their series a tight bandage about the head, interfering with the cir-

11. Northfield, D. W. C.: Some Observations on Headache, Brain **61**:133, 1938.
12. Simons, D. J.: Personal communication to the authors.
13. Weiss, S., and Davis, D.: The Significance of Afferent Impulses from the Skin and the Mechanism of Visceral Pain, Am. J. M. Sc. **176**:517, 1928.

culation to the scalp, did not alter the intensity or quality of the histamine headache. Experiments done in this laboratory, however, indicate that some modification in the intensity and the distribution of the headache may occur as a result of this procedure.

EXPERIMENT—A sphygmomanometer cuff with a firm bandage fitted over it was applied about the head of 3 subjects. Histamine phosphate was then injected intravenously, and when the headache had made itself manifest, the cuff was inflated to well above the systolic blood pressure (200 mm. of mercury). The then tight and uncomfortable cuff caused the histamine headache to be imperceptible, considerably diminished or indistinguishable from the discomfort produced by the tight band. With release of the pressure of air in the cuff the histamine headache again became apparent and seemed to have its former intensity.

In connection with these experiments, the experience of Sutherland,[14] working in this laboratory, affords further relevant data. In a series of 9 subjects, he placed a sphygmomanometer cuff about the head, padding the region near the temporal arteries so that after inflation to 200 mm. of mercury the temporoparietal region of the scalp, possibly also much of the rest of the scalp, received no blood. In no subject after histamine injection was the headache as intense as before the application of the cuff, and in all subjects headache when experienced was chiefly frontal. In 2 the headache was not discernible from the initial discomfort of the tight cuff.

In the light of the hypothesis advanced by Hardy, Wolff and Goodell [15] that the threshold of sensation to a given pain is raised by the introduction of a second pain, these data may not be interpreted as signifying that the diminution of headache by a tight bandage is due to the obstruction of scalp arteries, which thus prevents painful dilatation. It was demonstrated by these investigators in experiments on 3 subjects that if a painful stimulus produced by the concentrated thermal radiation from a 1,000 watt lamp was allowed to fall on the forehead during the histamine headache it was possible by increasing the intensity of the secondarily induced pain to reach a level that made the underlying headache imperceptible. In short, a secondarily induced pain of graduated intensity approximating that of the histamine headache diminished the intensity of the latter. This phenomenon will be alluded to later in discussing which arteries are chiefly responsible for the intensity of histamine headache.

The effect of a tight bandage may thus have two explanations: (1) painful dilatation of scalp arteries is prevented and (2) what is more likely, the threshold of pain is raised by application of the tight and slightly painful bandage.

Direct Manipulation of Arteries of the Scalp.—In order to learn more about the role of the superficial arteries in histamine headache, further experiments were performed as follows:

14. Sutherland, A. M.: Personal communication to the authors.

15. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Studies in Pain Sensation, unpublished data.

EXPERIMENT 1.—In 5 subjects the effect of manual obliteration of the temporal artery on the histamine headache was especially investigated. In 2 subjects the obliteration seemed to reduce the intensity of the headache on that side; in 3 subjects it had little or no effect. Pressure on the nearby structures had no effect.

EXPERIMENT 2.—One of us (G. S.) serving as subject, the entire frontal, temporal and parietal areas on the right side of the scalp were thoroughly infiltrated with a 1 per cent solution of procaine hydrochloride, the frontal, temporal and supraorbital arteries themselves being thus surrounded with the anesthetic. This resulted in analgesia over the entire left side of the head in an area bounded by the nose, the ear and the vertex. Subsequent intravenous injections of 0.1 mg. of histamine phosphate produced severe headache in the frontotemporal region, bilaterally, with no perceptible difference on the two sides.

EXPERIMENT 3.—In 4 patients ligation of the temporal artery on one side did not alter the quality of the histamine headache on the two sides of the head (see section on "Middle Meningeal Arteries").

EXPERIMENT 4.—Histamine phosphate was injected directly into the temporal artery in 2 of us (G. S. and H. G. W.). In the first subject the agent was injected into the artery through the intact skin; in the other the right temporal artery was surgically exposed and the histamine injected directly into its lumen. The results by the two methods were identical. The observations on the second subject follow.

The right temporal artery, after surgical exposure, was suitably held by means of a ligature placed about it. Manipulation of the artery was painful. Pulling the artery from below upward, while it was being immobilized in preparation for insertion of the needle, caused pain in the upper teeth. When the artery was pulled down from the temple the pain was felt in the temple and deep behind and in the eye. Inserting the needle into the artery was very painful. The pain that resulted from spreading the tissues in the neighborhood of the artery was also intense.

When 0.1 mg. of histamine phosphate was injected into the temporal artery, the first sensation was unilateral diffuse burning in the temporal region as high as the margin of the temporal bone (twenty-one seconds after injection[16]). The pain became more severe and was soon of a dull aching nature and more widespread than that due to the puncture of the artery. This sensation was followed by the usual taste (after twenty-six seconds) and then by a slight decline in the intensity of the headache (after thirty-six seconds). A unilateral flush, heretofore barely perceptible, now (after forty-four seconds) became readily visible, persisting for three minutes. The headache then returned in greater intensity (after fifty seconds), to remain unilateral and in the general area mentioned, namely, the temporal and parietal regions. It became a deeper, poorly localized headache, but remained unilateral; it was dull and throbbing, but still not severe. It covered the right temporoparietal region, extending upward about two thirds of the way to the vertex, posteriorly to the anterior border of the occipital area and anteriorly to the lateral margin of the frontal area. After two minutes the

16. All time intervals are given in terms of the period after beginning of the injection. It took six seconds to inject all of the histamine.

deeper component increased in intensity and was felt also in the frontal region. Most of the pain remained unilateral, but later (two minutes and thirty seconds) there was slight headache on the other side. The deep, aching, throbbing pain was still present in the temporoparietal and frontal regions on the side of the injection. The scalp in the region of the injection was "sore" to pressure, and compression of the temporal artery here increased the pain, but reduced it in the remainder of the involved area. The headache was gone three minutes and thirty seconds after the injection.

These experiments suggest that the temporal artery, possibly also the frontal, supraorbital and occipital arteries, may participate in the histamine headache.

The work of Hardy, Wolff and Goodell [16a] indicates that spatial summation of pain does not occur. Expressed more simply, this hypothesis states that the total effect of several intensities of pain acting simultaneously is equal not to their sum but merely to the intensity of the severest pain. In other words, on the assumption that several groups of arteries are involved in histamine headache, it is likely that the intensity of the headache is determined by those arteries which make the greatest contributions to pain.

It seems probable from the data presented that the contribution of the extracranial arteries does not determine the intensity of the histamine headache. Though local headache was produced by direct injection into the temporal artery, it must be remembered that a comparatively high concentration of histamine was permitted to act directly on the arterial wall and that extreme stretching probably occurred. Under such circumstances, an artery known to be sensitive to pain [2] might well give rise to local headache. But during generalized headache following injection of histamine into the antecubital vein, in the absence of such extreme local dilatation of extracranial arteries, it is doubtful whether the contribution made by these arteries predominates.

MIDDLE MENINGEAL ARTERIES

Inferences concerning the part contributed to histamine headache by pain impulses from the middle meningeal artery were drawn from experiments to be discussed in another connection in the section on experimental series II. Seven subjects in this series had incomplete rhizotomy of the trigeminal nerve for tic douloureux.

In all 7 patients the approach to the gasserian ganglion and its root included ligation and section of the middle meningeal artery and destruc-

16a. Hardy, J. D.; Wolff, H. G., and Goodell, H.: Studies on Pain: A New Method for Measuring Pain Threshold; Observations on Spatial Summation of Pain, J. Clin. Investigation **19**:649, 1940.

tion, over 1 to 2 cm., of the periarterial nerve fibers. (The fact that "bleeding back" occurred demonstrated that the ligated arteries were subsequently filled with blood.) If, therefore, in these subjects there was no difference in an induced histamine headache on the two sides, the inference could be drawn that the middle meningeal artery did not make a perceptible contribution to the pain of the histamine headache. The interval between ligation and injection of histamine varied in the 7 cases, but in no instance was it great enough to afford regeneration of the sensory fibers.

EXPERIMENT 1.—To the 7 subjects mentioned, histamine was administered intravenously. The headache which resulted was equal on the two sides of the head. Moreover, for 4 of the 7 patients the operative approach involved ligation of the ipsilateral temporal artery. As indicated in the preceding section (page 705), these 4 subjects did not differ in their reactions to histamine in any way from the others, who had the temporal artery intact.

Though the pain contributed by the middle meningeal arteries is not as great as was first suggested by Pickering and Hess,[9a] one may not infer that they are not involved. It is evident, however, that the absence of a pain-sensitive middle meningeal artery on one side does not appreciably decrease the intensity of the headache. Also, the contribution of pain from the temporal artery can similarly be considered imperceptible.

The evidence just presented suggests that the dural arteries are not the major contributors to the pain of histamine headache. It also adds further weight to the opinion previously expressed regarding the minor role of the extracranial arteries. Observations of Northfield [11] support these views. After injection of histamine into the internal carotid artery in 6 cases, that investigator obtained homolateral headache in 5 cases and no headache in 1. After injection of histamine into the external carotid artery in 6 cases, headache was absent in 5 and was faint and generalized in 1.

CEREBRAL ARTERIES

By a process of elimination it is possible to infer that the cerebral arteries are the chief sources of histamine headache. This view is based, in summary, on the following data which have been presented: (1) demonstration of afferent nerves on the larger cerebral vessels, especially those near the base of the brain; [4] (2) observed cerebral vasodilation following injections of histamine; [10] (3) relief of histamine headache which results from increasing intracranial pressure,[9] (4) ineffectiveness of blocking afferent impulses from the superficial tissues of the scalp in diminishing histamine headache; [12] (5) ineffectiveness of anesthetizing

the extracranial arteries themselves; (6) lack of proof that compressing the arteries of the scalp reduces the intensity of histamine headache; (7) lack of appreciable decrease in histamine headache on one side following ligation of the middle meningeal or the temporal artery, or both arteries, on that side, and (8) development of homolateral histamine headache following the injection of the internal carotid artery, but not following injection of the external carotid.

The evidence thus far adduced indicates that many cranial arteries participate in headache, but that the cerebral arteries are the chief contributors to the pain of histamine headache and determine its intensity. The question as to which cerebral arteries are implicated may now be considered further.

That the circle of Willis at the base of the brain and the proximal portions of its main branches are pain sensitive has been demonstrated [17] on patients during cerebral exposure under local anesthesia. Furthermore, the pain is intense, definite and constantly localized. The branches of these vessels become insensitive as they spread over the convexity or become intracerebral arteries and arterioles.

Stimulation of the internal carotid and of the anterior, middle and posterior cerebral arteries causes pain within, behind or over the eye as far medial as the midline and as far lateral as the temporal region. Stimulation of pontile and internal auditory branches from the basilar artery causes pain behind the ear. Faradic stimulation of the vertebral and the basilar artery and the posterior inferior cerebellar branches near their origin causes pain in the occipital and the suboccipital regions.[17]

The headache due to histamine is distributed to a variable degree in different persons over the areas just described. It is usually worse in the frontal and the temporal region, but sometimes begins in the occipital and the suboccipital area and moves forward. It is to be expected, therefore, that histamine headache arises from branches of several main arteries to the intracranial cavity: namely, the vertebral arterial branches of the subclavian artery; the basilar artery, which is derived from a confluence of the two vertebral arteries; the posterior cerebral arteries, resulting from a bifurcation of the basilar artery, and, finally, the middle and anterior branches of the internal carotid artery.

SUMMARY AND CONCLUSIONS

It has been demonstrated that the arteries of the scalp are capable of contributing to histamine headache and that there may be variation in the contribution made by them in different persons, the implication of

17. (*a*) Ray and Wolff.[2] (*b*) Fay.[3a]

these arteries possibly adding to the distribution of the headache. Furthermore, evidence has been presented to show that the cerebral arteries are important sources of histamine headache and that in the absence of pain contributions from the extracranial and dural arteries the intensity of the histamine headache is not diminished.

Thus, since it has been demonstrated elsewhere that spatial summation of pain does not occur,[16a] it is justifiable to infer that the intensity of the headache is determined by the cerebral arteries. Moreover, it seems probable that the large arteries at the base of the brain, which include the internal carotid, the vertebral, the basilar artery and the proximal portions of their branches, are the primary sites of origin of pain in the headache resulting from histamine.

SERIES II

In the following experiments designed to demonstrate the pain pathways involved in histamine headache, headaches were induced by intravenous administration of histamine in subjects who had previously had section of various cranial and cervical nerves. Most of the patients had had partial or complete section of the sensory root of the fifth cranial nerve for trigeminal neuralgia. Others had had section of the seventh, eighth, ninth or tenth cranial nerve. Also studied were patients who had had section of cervical dorsal roots, patients who had disease of the bulb and of the cervical region of the cord and those who had had section of the sympathetic trunk.

Based on common knowledge concerning the distribution of pain fibers to the skin over the head and neck, the assumption was made that the face and head as high as the vertex are supplied chiefly by the fifth cranial nerve and that the back of the head and neck are supplied chiefly by the second and third cervical nerves. Analgesia in these regions was assumed to be due to destruction of the aforementioned respective pathways or their nuclei. Though other afferent pathways are believed to carry pain fibers from the head, such as the first cervical and the eleventh and twelfth cranial nerves from the occiput, and the seventh, ninth and tenth cranial nerves from the region in and just behind the ear, interruption of these pathways did not result in demonstrable analgesia. In these experiments, therefore, anatomic inferences as to which pathways were interrupted were based whenever possible on surgical visualization rather than on the area of analgesia.

Pickering and Hess [9a] reported that in normal subjects histamine headache affects both sides of the head equally; this we have confirmed. It usually begins in the forehead just above the orbits, occasionally in the

temples, and while remaining maximal there sometimes spreads over the vertex and frequently into the occipital region as it increases in severity. It may, however, begin in the occiput and move forward (fig. 1).

In this study, subjects with unilateral analgesia were chiefly employed. Thus the normal side served as a suitable control for the abnormal side in each case. Because in the normal person histamine headache was symmetric and equal on the two sides, the following assumption was made: If headache failed regularly to be induced in an analgesic area on one side of the head but occurred regularly in the corresponding area on the opposite intact side, the absence of headache on the analgesic side was due to the interruption of the afferent pathway conducting impulses interpreted as headache in that region of the head.

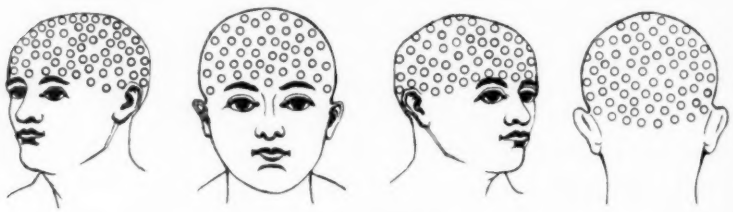

Fig. 1.—Site of headache, indicated by circles, following the injection of histamine in a normal person.

METHOD

Areas of anesthesia over the face, scalp and neck of the subject were carefully mapped out and recorded. Perception of pinprick and of cotton wool was routinely tested, as was also sensation of the cornea. The subject then lay on a stretcher in preparation for an intravenous injection of 0.1 mg. of histamine phosphate.

In order to be sure that the cranial arteries were stretched adequately during the experiments, photographic records of the pulsations of these arteries were made during each induced headache. This was done by means of an air-tight system connecting a tambour to a Frank capsule with a mirror on which was directed a beam of light. The tambour was affixed over the temporal artery. The transmitted pulsations were reflected from the mirror on a moving strip of film within a camera (Clark, Hough and Wolff [9b]).

Several control records of pulsations of the normal temporal artery with control readings of the pulse and blood pressure were made. The subject was carefully instructed in advance to note the exact sites and relative intensities of the headache which was to be induced. After administration of the histamine, while the arterial pulsations were being recorded and frequent readings of the pulse and blood pressure were being made, the subject was interrogated repeatedly as to the site and intensity of the headache. These data, together with the exact times, were recorded during the experiment. After subsidence of the headache, the experience was again carefully reviewed with the subject. In all cases of

induced histamine headache, the photographic record indicated substantial increase in the amplitude of pulsations of the temporal artery.

OBSERVATIONS

This series of experiments was performed on 20 subjects, who were separated into several groups according to the afferent pathways interrupted. The location of the histamine headache in each of these groups was as follows:

Partial Section of the Sensory Root of the Fifth Cranial Nerve with No Analgesia.—In 1 subject an incomplete rhizotomy of the fifth cranial nerve had

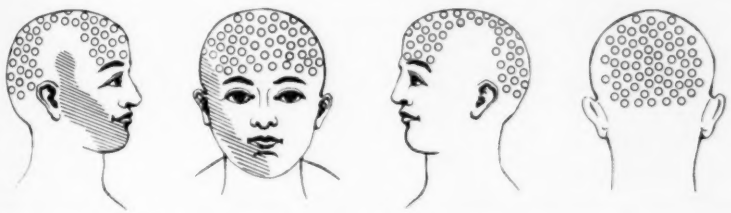

Fig. 2.—Areas of headache following the injection of histamine, and of analgesia to pinprick in a person who had had partial section of the sensory root of the fifth cranial nerve. In this figure and in the accompanying figures, the area of headache is indicated by circles; the area of analgesia by cross hatching.

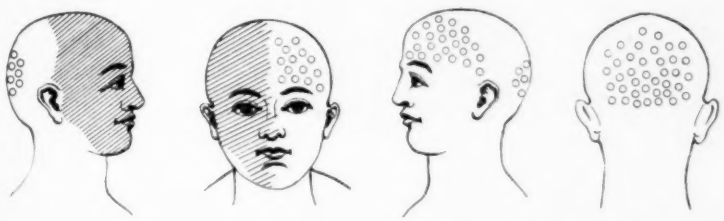

Fig. 3.—Areas of headache following the injection of histamine, and of analgesia to pinprick in a person in whom the sensory root of the fifth cranial nerve had been completely sectioned.

been performed, with resultant abolition of tic douloureux. Subsequently, no analgesia could be demonstrated. After injection of histamine the man had severe bifrontal headache.

Partial Section of the Sensory Root of the Fifth Cranial Nerve with Unilateral Analgesia of the Lower Part of the Face.—Six subjects had unilateral loss of cutaneous sensation in the lower portion of the face due to partial section of the sensory root of the fifth cranial nerve on one side, the outermost fibers of the root having been cut. After intravenous injection of histamine all these persons had bilateral headache. In 3 it occurred only in the frontal region, but in 2 it involved the entire head (frontal, temporal, parietal and occipital areas; figs. 2 and 4 *A*). The sixth patient had headache which was confined to the center of the front of the head, extending somewhat to both sides.

Complete Section of the Sensory Root of the Fifth Cranial Nerve with Unilateral Analgesia of the Whole Face and Anterior Half of the Scalp.—In 8 subjects as a result of complete section of the sensory root of the fifth cranial nerve, hemianalgesia of the face and of the anterior half of the scalp (including corneal anesthesia was found. In 7 of these subjects, headache was not induced in the frontotemporoparietal region of the head on the side on which the nerve had been cut, but was present elsewhere in the head (figs. 3 and 4 *B*). In 3 of the 7 it was induced only in the frontotemporoparietal region of the opposite side; in the remaining 4 it occurred both in the frontotemporoparietal region of the opposite side and in the back of the head on both sides. The eighth subject had headache in the frontoparietal region on both sides, being more severe on the side on which the nerve had been cut.

Pickering and Hess [9a] induced histamine headache in 3 patients in whom by surgical intervention cutaneous sensation over the area of

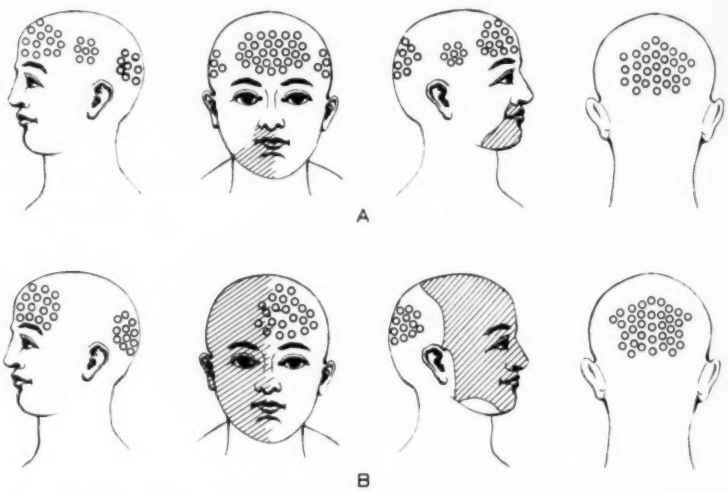

Fig. 4.—Areas of headache following the injection of histamine, and of analgesia to pinprick in a person who first had (*A*) partial section and then (*B*) complete section of the sensory root of the fifth cranial nerve.

distribution of the trigeminal nerve was completely abolished on one side. In all 3 headache was confined to the side of the head on which normal innervation was preserved.

Northfield [11] likewise injected histamine into 7 subjects who had had complete section of the sensory root of the trigeminal nerve on one side. In 3 persons the resulting headache was restricted to the forehead and temple of the opposite side and the back of the head on both sides. In 2 subjects headache was distributed over both sides of the front of the head, and in 1 of these it was worse on the side of the operation. In the remaining 2 persons no headache occurred, but in 1 of these injection of 10 cc. of air into the lumbar theca produced bilateral head-

ache in the back of the head, later involving only the front and side of the head on the normal side.

A comparison of the results described by Pickering and Hess and by Northfield with those obtained by us in cases of complete section of the sensory root of the trigeminal nerve shows incomplete agreement. In 7 of 8 subjects in the series reported here headache could not be induced in the analgesic region on the denervated side. Pickering and Hess found this to be true of all their 3 subjects. Northfield, however, obtained similar results for only 3 of 7 subjects. Of the remaining 4 subjects, 2 had headache on the denervated side and 2 had none at all. The results for the latter may be omitted from consideration on the basis of an insufficient histamine effect; unless a headache is actually induced by an adequate intravenous dose of histamine, it is not possible to draw inferences as to the effect of interruption of a given afferent

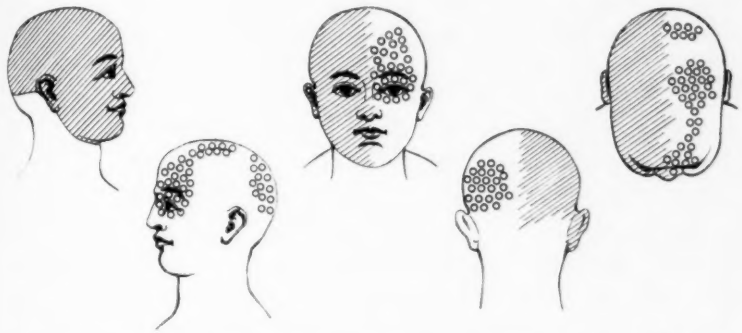

Fig. 5.—Sites of headache in a person in whom a lesion of the brain stem has produced complete hemianalgesia.

pathway on the site of headache. Northfield found, nevertheless, that in 1 of these 2 subjects headache produced by another means, namely, the injection of air into the spinal subarachnoid space, resulted in pain on only the normally innervated side of the front of the head and on both sides of the back of the head. Thus, in Northfield's series, 4 of 6 subjects had no pain in the denervated area but had it elsewhere in the head, whereas 2 had headache also on the denervated side.

In combining the results of our investigations with those of the other workers, it is seen that of a total of 17 subjects with complete section of the sensory root of the trigeminal nerve, 14 experienced no headache in the frontoparietal region on the side of the root section after injection of histamine, though all experienced it in other parts of the head.

Lesion of the Brain Stem and Upper Part of the Cervical Region of the Cord, with Hemianalgesia of the Head.—One subject had hemianalgesia of the face, forehead and scalp, including the occipital region, as a result of an injury

to the head. The lesion involved, among other structures, the descending sensory nucleus of the trigeminal nerve, including the upper cervical sensory levels of the cord. On injection of histamine this subject had severe headache in the frontal and occiptal areas on the normal side but none on the analgesic side (fig. 5).

Multiple Section of the Roots of the Cervical and Cranial Nerve with Hemianalgesia of the Head.—Two subjects with extensive infiltration of carcinoma (into the orbit and jaw, respectively) had had several nerves sectioned because of intractable pain. Both had had complete unilateral section of the sensory root of the fifth cranial nerve, the ninth cranial nerve and the sensory roots of the second and third cervical nerves. In addition, 1 had section also of the tenth cranial nerve and of the sensory root of the first cervical nerve. In neither was the pain induced by the carcinoma completely abolished. In each pain was present on the denervated side of the head before the experiment was begun. The pain seemed to become worse after the administration of histamine, though the induced headache was felt also on the other side of the head. Cooperation was poor, and the reports were difficult to evaluate.

Syringomyelia with Unilateral Occipital Analgesia.—In 1 patient occipital hemianalgesia had resulted from syringomyelia. After injection of histamime headache occurred "in the center of the back of the head" and slightly in the front of the head, but was most intense in the back on the normal side. On the analgesic side of the back of the head pain was absent.

Histamine headache was absent on one side of the back of the head in 2 subjects with lesions of the cervical portion of the cord and occipital analgesia (including the subject with complete hemianalgesia of the head mentioned on page 713). This evidence suggests that the cervical nerves are afferent pathways for impulses giving rise to occipital headache.

It is relevant to consider further the afferent pathway for some of the painful impulses from the occiput and the posterior fossa. Ray and Wolff [2] have shown that dural arteries of the posterior fossa, when stimulated with faradic current, produce pain in the occiput. Similarly, stimulation of the vertebral artery and the proximal segment of the posterior inferior cerebellar artery gives rise to pain in the occiput and suboccipital. The proximal segments of the pontile and the internal auditory artery are supplied by fibers stimulation of which causes pain behind the ear. Section of cranial and cervical nerves followed by stimulation of pain-sensitive structures in the posterior fossa indicated further, according to Ray and Wolff, that these structures are supplied chiefly by branches of the ninth and tenth cranial nerves and the first three cervical nerves.

Section of the Seventh Cranial Nerve.—In 1 patient extirpation of an acoustic neurinoma on the left side involved section of the left seventh and eighth cranial nerves close to the brain stem. The operation required a transverse incision across the back of the head at the level of the external occipital protuberance. At the time of this experiment the patient had complete anesthesia of the occipital region from the external occipital protuberance to the vertex, left nerve deafness and complete palsy of the left side of the face. The headache following intravenous injection of histamine was severe, bilateral and equal on the two sides and was limited to the frontotemporal region.

This observation demonstrated that the seventh cranial nerve does not play a major part in conduction of the pain impulses resulting from effects of histamine on cranial arteries, since severe frontal and temporal headache was experienced by the subject when the nerve was sectioned close to the brain stem. This fact is of interest, since it has been shown that afferent nerves from the pial arteries enter the brain stem through the seventh cranial nerve (Chorobski and Penfield [8]). Apparently, this nerve is not an important afferent path for pain.

The effect of section of the eighth cranial nerve can be waived in a discussion of histamine headache, since it has been repeatedly demonstrated (Ray and Wolff [2]) that no pain results from stimulation of the central end of this nerve.

Section of the Glossopharyngeal Nerve.—In 1 subject the glossopharyngeal nerve had been sectioned as a therapeutic measure for anomalous tic douloureux. After section the patient was relieved of the symptoms and had poorly defined analgesia in the back of the throat and over the tonsil. Intravenous injection of histamine phosphate was associated with the usual generalized headache, which did not differ on the two sides of the head.

It may be inferred, therefore, that the glossopharyngeal nerve does not play a major role in conveying impulses essential to histamine headache.

It is, however, impossible to exclude both the seventh and the ninth cranial nerves, as taking no part in conduction of pain, for, according to the hypothesis stated previously, the absence of minor contributions to the headache could not be appreciated if the most intense contribution, conveyed along other pathways, was still present.

Section of the Sympathetic Trunk.—One subject, who had had bilateral section of the cervical portion of the sympathetic trunk at the stellate ganglion for Raynaud's disease, experienced severe and generalized headache after injection of histamine. A second patient, who had had bilateral section of the second and third thoracic white rami communicantes, in addition to transection of the thoracic portion of the sympathetic trunk beneath the third ganglion, also had generalized headache after injection of histamine.

Although Dandy [18] produced termination of severe hemicrania in 2 patients by resecting the inferior cervical and the first thoracic ganglion on the side of the pain, both Northfield [11] and Pickering and Hess,[9a] on injecting histamine into patients after this operation, found that resection of the ganglia did not affect the usual distribution of histamine headache.

The fact that the patients with unilateral analgesia in the occipital and suboccipital regions have less or no pain in these regions after

18. Dandy, W.: Treatment of Hemicrania by Removal of the Inferior Cervical and First Thoracic Sympathetic Ganglia, Bull. Johns Hopkins Hosp. **48**:357, 1931.

administration of histamine, together with the work of Ray and Wolff,[2] suggests that the sensory roots of the upper cervical nerves (first, second and third) and the ninth and tenth cranial nerves are afferent pathways for these sensations. However, section of the fifth, seventh, ninth and tenth cranial nerves and the sensory roots of the first, second and third cervical nerves did not eliminate the headache due to histamine or that due to invasion of the skull and dura by carcinoma. Also, section of the seventh or the ninth cranial nerve alone failed to diminish histamine headache perceptibly. It is therefore evident that the afferent pathways are numerous, and that to ascribe the entire function of the sensation of headache to one or another nerve is an unjustified simplification.

SUMMARY

1. Of 15 subjects in whom afferent impulses from the superficial tissues of the scalp on one side were blocked by procaine, histamine headache in 4 and headache due to pneumoencephalographic examination in 11 were the same on the two sides of the head.

2. In 12 subjects obliteration of the circulation of the scalp by a blood pressure cuff modified the intensity of the histamine headache. That the reduction in pain was due to raising the pain threshold by introducing a second pain (the tight cuff) is offered as a likely hypothesis. Of 5 subjects, obliteration of the temporal artery by manual compression reduced the intensity of the histamine headache on that side in 2 but had no effect in 3. Complete subcutaneous infiltration with procaine hydrochloride of half the anterior part of the scalp (frontal, parietal and temporal areas on one side), including presumably all the vessels of the scalp in that area, did not prevent severe histamine headache in the frontotemporal region, bilaterally, which was of equal intensity on the two sides.

3. Injection of histamine directly into the temporal artery resulted in homolateral temporoparietal headache in 2 subjects.

4. Ligation of the temporal artery on one side in 4 subjects and of the middle meningeal artery on one side in 7 subjects did not influence the intensity of the headache experienced on the two sides after injection of histamine.

5. In 7 subjects who had partial section of the sensory root of the fifth cranial nerve on one side (resulting in unilateral analgesia of the lower part of the face in 6), histamine headache occurred bilaterally.

6. In 7 of 8 patients who had complete section of the sensory root of the fifth cranial nerve (resulting in unilateral hemianalgesia of the face and anterior half of the scalp), histamine headache was not induced on the denervated area, but did occur elsewhere in the head.

7. In a subject with complete hemianalgesia of the face and head (resulting from a head injury), strictly unilateral hemicrania on the normal side of the head was induced by histamine.

8. Histamine headache was absent in the back of the head on one side, but was present elsewhere in the head in 2 subjects with lesions of the cervical portion of the cord, causing unilateral occipital analgesia.

9. Section of the seventh and the ninth cranial nerve, respectively, in 2 subjects did not affect the bilateral equality of the headache induced by histamine.

10. Section of both sympathetic trunks in 2 subjects (cervical portion in 1 and thoracic portion in the other) had no effect on subsequently induced histamine headache.

CONCLUSIONS

1. Histamine headache does not depend on the integrity of sensation from the superficial tissues.

2. The extracranial and dural arteries play a minor role in contributing to the pain of histamine headache.

3. Cerebral arteries, principally the large arteries at the base of the brain, including the internal carotid, the vertebral and the basilar artery and the proximal segments of their main branches, are chiefly responsible for the quality and intensity of histamine headache.

4. Although there may be other less important afferent pathways for the conduction of impulses interpreted as headache following injection of histamine, (*a*) the fifth cranial nerve on each side is the principal afferent pathway for headache resulting from dilatation of the supratentorial cerebral arteries and felt in the frontotemporoparietal region of the head, and (*b*) the upper cervical nerves are the most important afferent pathways for headache resulting from dilatation of arteries of the posterior fossa and felt in the occipital region of the head.

THE HUMAN PYRAMIDAL TRACT

II. A NUMERICAL INVESTIGATION OF THE BETZ CELLS OF THE MOTOR AREA

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With few exceptions, elementary and clinical textbooks of human neurology describe the pyramidal tract fibers as arising solely from the Betz, or gigantopyramidalis, cells of the motor area (area 4). Some investigative work, however, suggests that this may not be the case. Campbell,[1] counting only every fifth section which came from the microtome, roughly estimated the number of Betz cells in the motor area of man as 25,000. Using the Bielschowsky technic, Weil and Lassek[2] calculated the number of corticospinal fibers entering the spinal cord as 250,000, or approximately ten times the number of cells reported. Recently, Lassek and Rasmussen,[3] employing the silver technic of Davenport and his co-workers,[4] reported that slightly over 1,000,000 of these axons descended into the cord on one side in each of 3 brains. In view of this marked discrepancy, an attempt has been made to determine, as exactly as possible, the number of Betz cells in the motor area of the human cerebral cortex.

In addition, determinations of the distribution of the Betz cells in the upper, middle and lower thirds of area 4, their quantitative relation to the exposed cortical surface and to the central sulcus and, finally, the numerical difference in the cells on the right and on the left side have been included in the undertaking.

From the Department of Anatomy, Medical College of the State of South Carolina.

1. Campbell, A. W.: Histological Studies on the Localization of Cerebral Function, Cambridge, England, University Press, 1905.

2. Weil, A., and Lassek, A. M.: The Quantitative Distribution of the Pyramidal Tract in Man, Arch. Neurol. & Psychiat. **22**:495-510 (Sept.) 1929.

3. Lassek, A. M., and Rasmussen, G. L.: The Human Pyramidal Tract: A Fiber and Numerical Analysis, Arch. Neurol. & Psychiat. **42**:872-876 (Nov.) 1939.

4. Davenport, H. A.: Staining Paraffin Sections with Protargol: Experiments with Bodian's Method; Use of n-Propyl and n-Butyl Alcohol in Hofker's Fixative, Stain Technol. **13**:147-160, 1938. Davenport, H. A.; McArthur, J., and Bruesch, S. R.: Staining Sections with Protargol: The Optimum p_H for Reduction; a Two-Hour Staining Method, ibid. **14**:21-26, 1939.

MATERIAL AND METHODS

The left and right motor areas of a Negress aged 22 were removed; each was divided into four blocks and embedded in pyroxylin. A total of 5,000 complete serial sections, or about 2,500 from each side, were cut sagittally at 35 microns, kept in order and stained with cresyl violet. The nucleoli of the Betz cells were then counted seriatim.

Although the Betz cells are the most conspicuous cells in the cerebral cortex, there is great variability in their magnitude. The question arose early as to what features are characteristic of such a cell body. The following criteria were used: The cell must be situated in the infragranular layer of the motor area of the cortex, be large and pyriform, possess abundant tigroid material, which has a marked affinity for the stain and, finally, have a spherical nucleus which is small in proportion to the size of the cell body. In general, all cells between 900 and 4,000 square microns in area, shrinkage being taken into account, with the foregoing features were included in the count. To me, the cells that fell approximately within these measurements seemed morphologically alike, their only difference being in size.

TABLE 1.—*Number of Betz Cells Counted in the Upper, Middle and Lower Thirds of the Right Motor Area (Area 4) of a 22 Year Old Negress*

Region of Area 4	Number of Betz Cells	Percentage
Upper third	25,822	75.5
Middle third	6,130	17.9
Lower third	2,231	6.6
Totals	34,183	100.0

RESULTS AND COMMENT

A total of 34,562 Betz, or gigantopyramidalis, cells was counted in area 4 of the left hemisphere. Of these 24,948 (72.2 per cent) were present in the upper third, 7,292 (21.1 per cent) in the middle third and 2,322 (6.7 per cent) in the lower third.

In area 4 of the right side a total of 34,183 such cells was counted, which were distributed as follows: upper third, 25,822 (75.5 per cent); middle third, 6,130 (17.9 per cent), and lower third, 2,231 (6.6 per cent). There was thus a minor difference in total numbers of 1.1 per cent in favor of the left side. From general examination, Betz [5] concluded that the cells which now bear his name were more numerous in the right side of the cortex. Campbell,[1] on the other hand, stated that this observation was open to grave doubts; the results of my investigation support his view.

Of the 34,562 Betz cells in area 4 of the left side, only 6,182, or 17.9 per cent, were from the exposed cortical surface. The remaining

5. Betz, W.: Anatomischer Nachweis zweier Gehirncentra, Centralbl. f. med. Wissensch. **12**:578-580 and 594-599, 1874.

28,380, or 82.1 per cent, were hidden mostly in the central sulcus, while a few occupied smaller precentral sulci. The left central sulcus measured 104 mm. in length and as much as 20 mm. in depth. The anterior wall of the rolandic fissure in man is thus an extensive area and is the site of the majority of the Betz cells. Of the cells from the cortical surface, 5,734 (92.8 per cent) were in the upper third of the motor area, 448 (7.2 per cent) in the middle third and none in the lower third. Of the 28,380 "buried" or fissure cells, 19,214 (67.7 per cent) were in the upper third, 6,844 (24.1 per cent) in the middle third and 2,322 (8.2 per cent) in the lower third.

The lower half, approximately, of area 4 in the brain examined had no Betz cells on the periphery; therefore, contact with these cell bodies could not easily have been made directly with stimulating electrodes.

TABLE 2.—*Number of Betz Cells Observed on the Exposed Cortical Surface and Buried Within the Central and Smaller Precentral Sulci of the Left Motor Area (Area 4) of a 22 Year Old Negress*

Region of Area 4	Total Number of Betz Cells	Number of Surface Cells	Number of Buried Cells	Percentage of Surface Cells	Percentage of Buried Cells
Upper third	24,948	5,734	19,214	23.0	77.0
Middle third	7,292	448	6,844	6.1	93.9
Lower third	2,322	0	2,322	0.0	100.0
Totals	34,562	6,182	28,380	17.9	82.1

If the deeply concealed gigantopyramidalis cells of this locality were responsible for its excitable properties, it seems likely that they achieved their effect through diffusion of current.

It is probable that there are individual and racial variations in the relations of the Betz cells to the visible cortex and central sulcus, since the cytoarchitectural maps of a number of investigators show area 4 extending rostrally from the central sulcus throughout its mediolateral extent.[6] The schematic drawing of Bucy [6a] seems to represent most closely the topography of the Betz cells in my specimen.

Since more than 1,000,000 corticospinal axons, of variable size but mostly of small caliber, were calculated to enter the spinal cord on one side in the specimen used for the present investigation,[3] the results here

6. (*a*) Bucy, P. C.: Frontal Lobe of Primates: Relation of Cyto-Architecture to Functional Activity, Arch. Neurol. & Psychiat. **33**:546-557 (March) 1935. (*b*) Economo, C. F., and Koskinas, G. N.: Die Cyto-architektonik der Hirnrinde des erwachsenen Menschen, Berlin, Julius Springer, 1925. (*c*) Brodmann, K.: Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellbaues, Leipzig, Johann Ambrosius Barth, 1909. (*d*) Foerster, O.: The Motor Cortex in Man in the Light of Hughlings Jackson's Doctrines, Brain **59**:135-159, 1936. (*e*) Campbell.[1]

obtained are added evidence that the Betz cells can contribute only 2 or 3 per cent of the total number of pyramidal tract fibers. The opinion stated in most elementary and clinical textbooks of neurology that the gigantopyramidalis cells give origin to the fibers of the pyramidal tract has its foundation, I believe, in the investigation of Holmes and May,[7] who studied reactionary chromatolysis and atrophy of cells after division of the pyramidal tract in the upper cervical region (hemisection) in a series of mammalian brains and in 2 suitable human specimens. They did not localize their lesions in the pyramidal tract itself, nor did they consider the possibility of subcortical centers in their quest for its cells of origin.

The Betz cells, because of their conspicuousness, greater area, higher metabolic rate and larger quantity of tigroid material, would show prominent reactionary changes, while changes in the smaller cells might be more difficult to evaluate. If it is true that the Betz cells are the only cellular elements giving origin to the pyramidal fibers, one would expect to find about 30,000 such axons on the basis of cell counts by Campbell [1] (25,000) and Lassek (34,000). In order to emphasize the unlikelihood of this, and by way of comparison, it can be mentioned that such a low-ranking mammal as the Virginia opossum has approximately 75,000 corticospinal fibers,[8] which is over twice the number of Betz cells in man. Even the mouse has about 32,000 pyramidal tract fibers at a level just rostral to the motor decussation.

I believe that the gigantopyramidalis cells contribute only the largest fibers to the pyramidal bundle of man. Big cells above probably have big fibers below. There are instances in other parts of the central nervous system of big motor cells which give off large, myelinated axons. My belief is further strengthened by the fact that there is a close correlation between the number of Betz cells and the number of large fibers of the pyramidal tract. Häggqvist's [9] observations in the monkey support this view. In his hands, removal of area 4 caused degeneration of only the largest fibers within the pyramids. He expressed the opinion that five sixths of the pyramidal fibers arise elsewhere than in area 4. His results are evidence against the axon of a Betz cell dividing into a number of descending fibers which course downward within the pyramids. In my laboratory, using the silver rather than the Marchi technic, I have found large numbers of corticospinal fibers in the pyramids of monkeys after removal of either area 4 or area 6. These results are

7. Holmes, G. H., and May, W. P.: On the Exact Origin of the Pyramidal Tracts in Man and Other Mammals, Brain **32**:1-42, 1909.

8. Lassek, A. M., and Rasmussen, G. L.: A Comparative Fiber and Numerical Analysis of the Pyramidal Tract, J. Comp. Neurol. **72**:417-428, 1940.

9. Häggqvist, G.: Analysis of Fibers of the Pyramidal Tract, Acta psychiat. et neurol. **12**:457-466, 1937.

given with reservations because histologic studies have not yet been made of the regions of extirpation. At this stage of the investigation, it seems to me that Häggqvist may be correct in his assumption that a large part of the corticospinal fibers in the monkey originate elsewhere than in area 4. If it should eventually be proved that both the pyramidal and the extrapyramidal projections receive fibers from two or more sources, then there is available a good neurologic explanation of why compensation occurs so rapidly throughout almost the entire mammalian kingdom when extirpations are made of parts of the central nervous system.

Foerster [10] stated that the pyramidal tract has "fast train" connections between the cortex and the cord and all other motor pathways originating in the cortical areas have "slow train" connections between the same regions. He expressed the belief that this difference in the speed of conduction is due to the fact that the pyramidal pathway is uninterrupted, while the extrapyramidal pathways have synaptic connections in subcortical centers. On the basis of the anatomy of area 4 and the pyramids, I believe that the "fast train" conductors in this system are the Betz cells and the largest fibers in the pyramids. This leaves unaccounted for the vast number of small fibers present in the pyramidal tract, which must be slowly conducting units.

One of the puzzling features of both the right and the left motor area in the specimen studied is that about three quarters of the Betz cells were congregated in the region of the cortex which is said to control the muscles of the lower extremities. This distribution agrees with Campbell's [1] observation that "it is evident that the majority of the cells, certainly more than half, reside above the level of the annectant buttress." The table on page 35 of his book indicates that most of the Betz cells are situated in the upper or medial third of area 4. If the superior third of the motor area controls the muscles of the lower part of the body, these muscles evidently require more and larger Betz cells than those of the upper appendages.

Three explanations can be advanced for the large caliber of the Betz cells:

1. Hughlings Jackson [11] expressed the belief that the magnitude of the motor cell varies according to the size of the muscle it controls, or, preferably, that it is in proportion to the "size of the movement." If one agrees with Jackson, one must hypothesize that the pyramidal tract fibers arise entirely from small cells, since they are thought to control the fine rather than the gross movements. Although most of the pyramidal tract fibers may arise from cells smaller than those of the Betz

10. Foerster, O.: The Cerebral Cortex in Man, Lancet **2**:309-312, 1931.

11. Jackson, J. H.: The Lumleian Lectures on Convulsive Seizures, Brit. M. J. **1**:765-771, 1890.

type, Jackson's theory, as I interpret it, would leave no role for the Betz cells to play in pyramidal conduction.

2. Lewis [12] expressed the thesis that "the greater the distance along which a nerve cell has to transmit its energy the larger will that nerve cell probably be." If this were true, then all the Betz cells in the upper part of the motor area should be larger than all the cells in the lower portions. This was by no means the case in the specimen examined. There is great variability in the magnitude of the Betz cells in any one region of area 4. It is only when the average is determined that it can be said that the cells in the upper third are bigger than those in the middle or the lower third.

3. The third theory, as cited by Fulton,[13] states that the size of the cell body depends on the extent of the motor unit innervated, or, in other words, the number of internuncial neurons with which it connects. If this were true, the Betz cells in the upper third of area 4 should make synaptic connections with more intercalated neurons, because the cells, on the average, are larger and more plentiful. Then, the Betz cells would have fewer connections with the anterior horn cells of the cervical enlargement, where one would expect widespread neurologic synapses to be in order. In man, Weil and Lassek [2] calculated that 50 per cent of the pyramidal tract fibers terminate in the cervical region of the spinal cord. Yet, the area of the motor cortex supposed to innervate the cervical anterior horn cells is notably deficient in the number and size of Betz cells. None of these theories seem to fit in perfectly with the size and distribution of the Betz cells and pyramidal fibers and the known facts concerning them.

Scarff [14] recently made an interesting report on localization within the motor area of the human cortex. He stated:

> . . . in man the so-called motor cortex has migrated to a higher position on the lateral convexity of the cerebral hemisphere than it occupies in any of the other primates, so that as a rule the centers for primary movements of the upper extremity extend up to the superior margin of the hemisphere, while in most instances the lower extremity is entirely unrepresented on the lateral surface of the cerebrum.

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12. Lewis, B.: On the Comparative Structure of the Cortex Cerebri, Brain **1**:79-86, 1878.

13. Fulton, J. F.: Physiology of the Nervous System, New York, Oxford University Press, 1938.

14. Scarff, J. E.: Observations Based on Electrical Stimulation Which Indicate That in Man Primary Centers for Movements of the Upper Limb Extend Upward on the Lateral Surface of the Cerebral Hemisphere as Far as the Superior Mesial Border and That Primary Centers for Movements of the Lower Limb Are Restricted to the Mesial Surface of the Cerebrum, Arch. Neurol. & Psychiat. **42**:968 (Nov.) 1939.

He arrived at these conclusions by stimulation of the superior mesial border of the hemisphere in 15 patients at operation.

In a preliminary study on the motor areas of the cortex of 3 macaque monkeys, I have calculated that there is a relatively lesser number of Betz cells in both the superior third of area 4 and the central sulcus than in the corresponding areas in man.[15] In the monkey about 50 per cent of all Betz cells are in the upper third; in man, 75 per cent. Only about 33 per cent of all Betz cells are situated within the central sulcus in the monkey, while in man there are approximately 82 per cent. In the phylogenetic gap between the monkey and man there is evidently a shift of the Betz cells, not only superiorly but also to a position within the depths of the central sulcus. It must be admitted that if Scarff's observation is correct, the majority of gigantopyramidalis cells are situated in a part of the motor cortex of man where they can exert a dynamic influence on the anterior horn cells of the cervical and lumbar enlargements of the spinal cord.

Since many far reaching physiologic conclusions have been drawn from experimental work on the monkey, I have in progress anatomic and experimental studies on the motor area and pyramidal system of this animal, using the numerical approach and the silver technic rather than the Marchi method.

CONCLUSIONS

There is no significant difference between the number of Betz cells on the right and on the left side of the cortex.

Thirty-four thousand, one hundred and eighty-three Betz cells were counted in area 4 of the right side of the human cerebral cortex. Of these, 75.5 per cent were in the upper, 17.9 per cent in the middle and 6.6 per cent in the lower third.

Thirty-four thousand, five hundred and sixty-two Betz cells were counted in the motor area of the left side of the cortex. Of these, 72.2 per cent were situated in the upper, 21.1 per cent in the middle and 6.7 per cent in the lower third.

Only 17.9 per cent of the total number of Betz cells were situated on the exposed cortical surface of the left motor area. The remaining 82.1 per cent were buried in the central and smaller precentral sulci.

In the brain examined, there were no Betz cells on the exposed surface in the lower one half, approximately, of area 4.

The Betz cells can contribute but 2 or 3 per cent of the fibers found within the pyramidal tract.

The size rather than the number of the Betz cells suggests that they may be of importance in pyramidal conduction.

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15. Lassek, A. M.: The Pyramidal Tract of the Monkey: A Betz Cell and Pyramidal Tract Enumeration, J. Comp. Neurol., to be published.

CHANGES IN THE NERVOUS SYSTEM FOLLOWING CARBON DISULFIDE POISONING IN ANIMALS AND IN MAN

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The problem of carbon disulfide poisoning has become increasingly important in recent years, owing to extensive use of this chemical in the rayon industry. Cases of poisoning due to exposure to carbon disulfide are reported from time to time, and the problem not infrequently arises whether the clinical and pathologic changes noted in a given case are in fact the result of carbon disulfide poisoning. For this reason an attempt has been made to gather all available data concerning the changes in the nervous system in carbon disulfide poisoning both in man and in the experimental animal, in order to determine whether there are specific alterations which result from this poisoning. In this paper the lesions of the nervous system in 9 dogs which were intoxicated with the chemical are reported and compared with the changes observed in cases of carbon disulfide poisoning in man.

REVIEW OF LITERATURE

Carbon Disulfide Poisoning in Man.—There have been many clinical reports of carbon disulfide poisoning, most of which have been reviewed recently by Gordy and Trumper.[1] There are surprisingly few necropsy reports of the changes in the human nervous system, and those which are available are contradictory. The first report of poisoning in man with necropsy is that of Forman [2] (1886), who merely recorded congestion of the cortical veins, but made no histologic studies. A similar gross study was made by Redaelli,[3] who also noted congestion and edema

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1. Gordy, S. T., and Trumper, M.: Carbon Disulfide Poisoning, J. A. M. A. **110**:1543 (May 7) 1938.

2. Forman, W.: Notes on a Fatal Case of Poisoning by Carbon Disulfide, Lancet **2**:118, 1886.

3. Redaelli, P.: Sull'anatomia patologica dell'avvellenamento cronico da sulfuro di carbonico, Boll. Soc. med.-chir., Pavia **38**:133, 1925.

of the brain. The first careful study of the nervous system was made by Quensel[4] (1904), who observed diffuse disease of the cortical ganglion cells, chiefly in the nature of chromatolysis, with particular involvement of the medium and small pyramidal cells. Swollen and shrunken ganglion cells were found in addition to the chromatolytic cells. The vascular endothelium was swollen, and fresh perivascular hemorrhages were seen in some areas. The glia cells and the cortical architecture were normal. An old area of hemorrhage was observed in the left calcarine area. The Purkinje cells of the cerebellum were chromatolytic; the hypoglossal and vagal-accessory nuclei and the anterior horn cells of the spinal cord showed scattered chromatolytic changes. The nervous system in this case, therefore, was diffusely affected, with ganglion cell changes of a nonspecific nature predominating and with swelling of the endothelium and scattered perivascular hemorrhages.

The only other study of changes in the human nervous system is that of Abe,[5] who observed a slight decrease in the number of cortical ganglion cells, large collections of gitter cells in the gyrus cinguli and the cornu ammonis, swollen endothelial cells, slight perivascular infiltration with lymphocytes and plasma cells in places and lipoid deposits in the walls of the vessels. The changes in the cortex were most pronounced in the frontal pole, the second and third temporal convolutions, the anterior half of the gyrus cinguli, the vicinity of the calcarine fissure and the cornu ammonis. The ganglion cells were affected by many sorts of processes. Degeneration of myelin sheaths was found in small islands. Changes were seen in the basal ganglia, but they were not pronounced. The large cells of the striatum were decreased in number, and the others were atrophied or sclerosed; the thalamus showed focal cell loss; the pallidum contained a few scattered gitter cells. In the cerebellum there were focal loss of the granule cells and myelin sheaths and a decrease in number of the Purkinje cells. The changes in the spinal cord consisted of loss of myelin, fatty degeneration and gliosis in the pyramidal tracts and anterior columns. There was also fatty degeneration of the anterior horn cells. Only slight changes were seen in the peripheral nerves. The changes reported by Abe were on the whole of a nonspecific nature and will be referred to subsequently.

Carbon Disulfide Poisoning in Experimental Animals.—Experimental observations on the effect of carbon disulfide poisoning are more definite than those reported in man, but they are still far from specific. Since there is no picture which is characteristic of the changes in the

4. Quensel, F.: Neue Erfahrungen über Geistesstörungen nach Schwefelkohlenstoffvergiftung, Monatschr. f. Psychiat. u. Neurol. **16**:48 and 246, 1904.

5. Abe, M.: Beitrag zur pathologischen Anatomie der chronischen Schwefelkohlenstoffvergiftung, Jap. J. M. Sc. Tr., VIII, Int. Med., Pediat. & Psychiat. **3**:1, 1933.

nervous system in this condition, the interest of clarity will best be served by an itemized account of the lesions which have been reported.

Changes in the ganglion cells have been observed by a number of investigators. While no specific mention is made of the extent of these changes, one is led to the assumption that they are universal. Fatty degeneration of the ganglion cells has been observed by Köster [6] and by Poincaré.[7] The former noted that the fatty changes involved first the dendrites and then the cytoplasm and nucleus. Poincaré also reported degeneration of ganglion cells without mention of the specific process involving the cells. Atrophy of the cells in the pallidum, striatum and substantia nigra in rabbits and guinea pigs was noted by Audo-Gianotti.[8] Shrinkage of the Purkinje cells and of the cortical ganglion cells was observed in rats by Wiley, Hueper and von Oettingen.[9] Baumana [10] noted changes in the ganglion cells of the cortex, basal ganglia, thalamus, brain stem and medulla in cats. The changes were severe and universal, consisting of swollen and vacuolated cytoplasm, with only slight damage to the neurofibrils. The Purkinje cells were damaged in 1 animal. Edema of the ganglion cells and of the perineuronal spaces has also been observed in cases of experimental carbon disulfide poisoning.

Perivascular hemorrhages have been observed in the white matter of the brain of rats by Wiley, Hueper and von Oettingen. Fragmentation of the myelin was reported by Köster and Poincaré. The latter described destruction of the myelin and its reduction to oil globules. Similar changes were seen in the spinal cord. Disease of the axis-cylinders accompanied the damage to the myelin sheaths. Poincaré reported also diffuse areas of softening in the white matter.

A few observers have noted changes in the blood vessels. Poincaré saw oil droplets in the small vessels of the brain, which he regarded as emboli. In some places the vessels were so filled with these droplets that they were greatly distended, and in some instances ruptured.

EXPERIMENTAL DATA

Material and Methods.—Nine dogs were subjected to the effects of carbon disulfide fumes. All the dogs were placed simultaneously in a chamber and were

6. Köster, G.: Beitrag zur der Lehre von der chronischen Schwefelkohlenstoffvergiftung, Arch. f. Psychiat. **32**:569, 1899.

7. Poincaré, L.: Recherches expérimentales sur les effets des vapeurs du sulfure de carbone, Arch. de physiol. norm. et path. **6**:18, 1879.

8. Audo-Gianotti, G. B.: La patologia dell'intossicazione professional da solfuro di carbonico, Rassegna di med. appl. lavoro indust. **3**:434, 1932.

9. Wiley, F. H.; Hueper, W. C., and von Oettingen, W. F.: The Toxic Effects of Low Concentrations of Carbon Disulfide, J. Indust. Hyg. & Toxicol. **18**:733 (Dec.) 1936.

10. Baumana, C.: Carbon Disulfide Intoxication of the Nervous System, Ztschr. f. d. ges. Neurol. u. Psychiat. **166**:568, 1939.

exposed to carbon disulfide fumes for eight hours a day, five days a week, for from two to six weeks. They were killed by the injection of air into the circulation.

While in the gas chamber the animals showed first intense excitement, but this gave way to drowsiness and apathy. Most prominent among the neurologic signs were tremor and ataxia. All the animals showed great difficulty in coordination, and eventually were unable to stand because of the extreme ataxia. Tremors and myoclonic movements of the limbs were prominent. Tremors of the head were common. The condition of the muscles varied; sometimes flaccidity was present, but sometimes spasticity developed and with it hyperactive tendon reflexes. Atrophy of the muscles was not infrequent, and was associated with loss of tendon reflexes.

Personality changes were observed in all the animals after exposure to the gas for a short time. All had been observed for some time before the experiment and had been found to be friendly. After exposure to the gas they became apprehensive, apathetic and sometimes unfriendly. They lost their usual friendliness and spent their time with heads drooped, backed to the wall; they objected to examination, usually whined and sometimes made attempts to bite.

The brain, spinal cord and peripheral nerves (brachial plexus and sciatic nerves) were fixed immediately on removal. Studies were made by the following methods: toluidine blue and cresyl violet stains, Weil's myelin sheath stain, Bodian's stain for axis-cylinders and stains for fat. All areas of the cortex, basal ganglia and brain stem were studied. The spinal cord was sectioned at several segments at all levels. The brachial plexus and sciatic nerves were studied in all cases.

Histologic Studies.—Damage to the nervous system was noted in all the animals. In general, the cortex was most severely injured; the basal ganglia were affected to an almost equal degree, while the cerebellum was less severely but none the less badly damaged by the carbon disulfide. The brain stem showed surprisingly little evidence of injury. The spinal cord was only moderately involved, while the peripheral nerves showed slight evidence of disease.

Meninges: The meninges were normal in most animals. Proliferative fibrous changes were observed in a few cases. Fibrosis of the meninges in the sylvian fissure was noted in 1 animal (dog 171); a few lymphocytes were scattered among the fibroblasts. In another animal a large number of lymphocytes and polymorphonuclear cells were seen at the base of the frontal lobe (dog 290). In all other animals the meninges were normal.

Cerebral Cortex: The cerebral cortex was badly damaged in all the animals. The injury was universal, all parts of the cortex being affected. No single area suffered more than another, except that the frontal lobes were somewhat more involved than other parts of the brain. The Betz cells of the motor cortex were invariably better preserved than other ganglion cells of the cortex. The cortical architecture was surprisingly well preserved in all the animals. No disruption of the normal cell

arrangement was noted. Only now and then was there focal loss of ganglion cells, but it was never striking and was discarded as being of no significance.

The changes in the ganglion cells were always of the same type, no matter what the degree of damage to the nervous system. They were uniform in all the animals and in all parts of the nervous system. In a few animals the cells in the upper cortical layers were most affected. They consisted of swelling of the cytoplasm and of the cell processes. Often the cell membrane was broken. The cytoplasm was frayed; the Nissl substance was pulverized and often entirely destroyed, and vacuoles

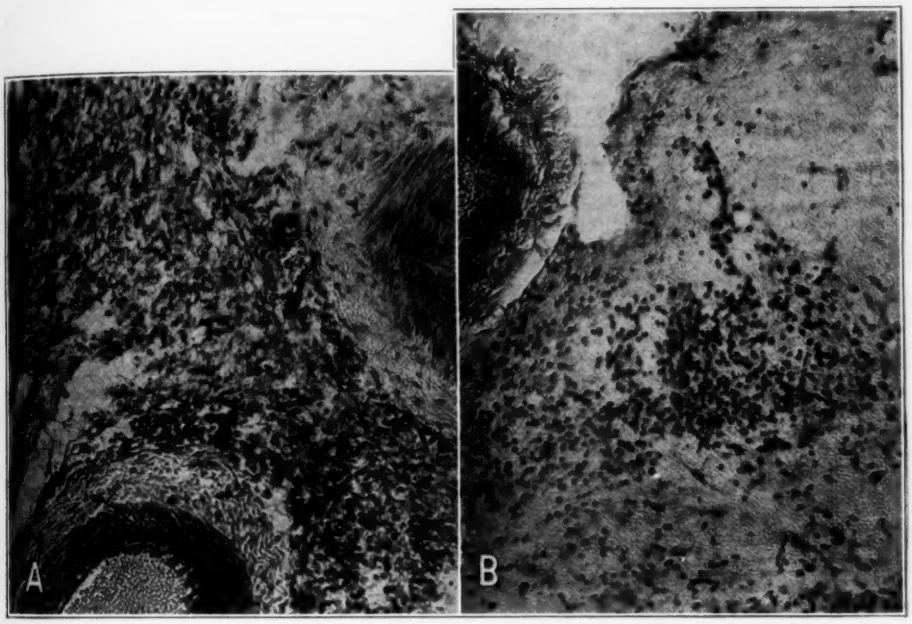

Fig. 1.—Meningeal changes in experimental carbon disulfide poisoning. *A*, thickened meninges from the base of the brain, the infiltration being largely by fibroblasts (dog 171). *B*, infiltration of the meninges over the cerebral hemispheres by lymphocytes (dog 290).

of varying size filled the cytoplasmic structure. Specific stains failed to reveal fat within the vacuoles. The nuclei and nucleoli were invariably swollen, and the nuclear membrane was often indistinct. In only 1 animal (dog 266) were more chronic cell changes seen. In some areas of the brain in this case the ganglion cells showed shrinking of the cytoplasm, tortuous dendrites, formation of vacuoles and clumped and heavily stained Nissl substance.

The changes in the glia of the cortex were less advanced than in the ganglion cells, and were entirely regressive. No proliferative

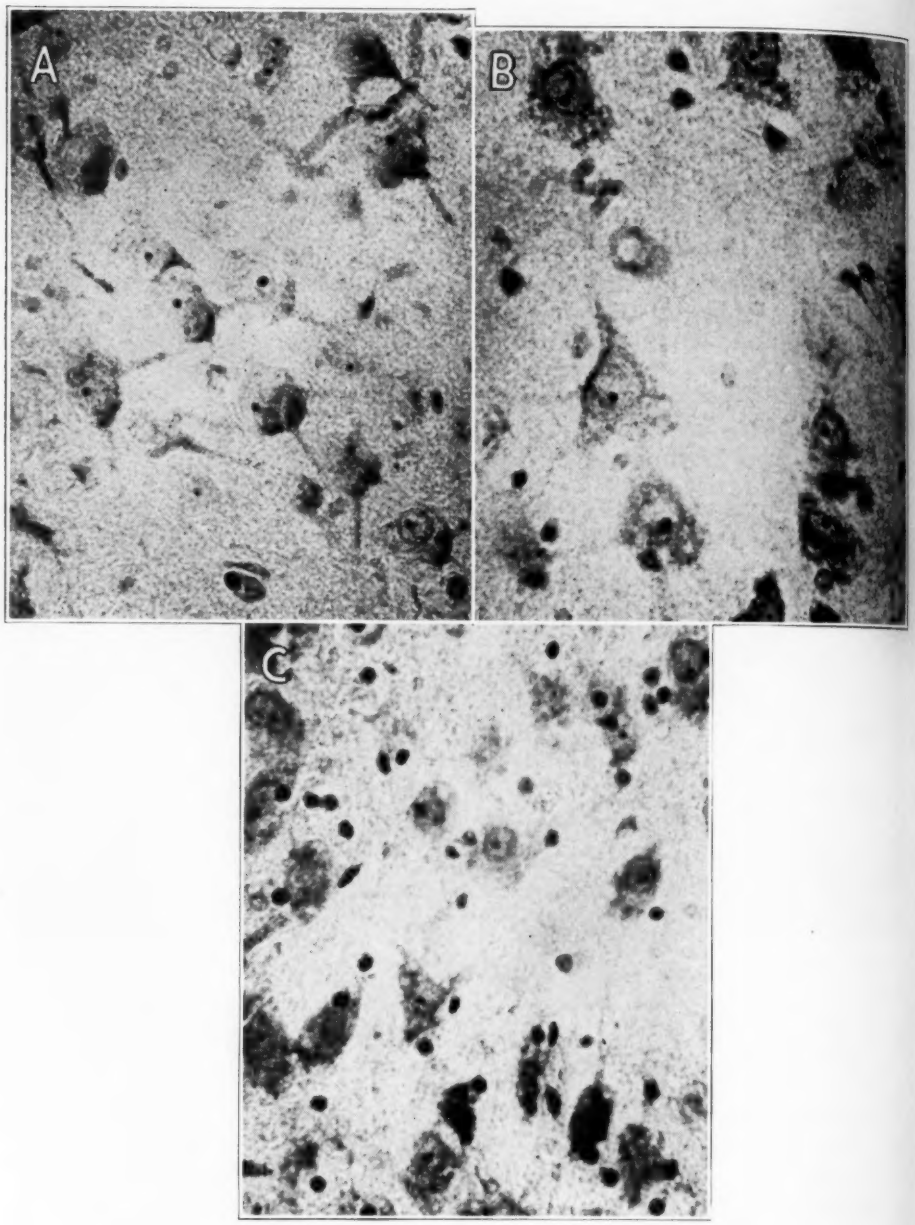

Fig. 2.—Changes in the ganglion cells in experimental carbon disulfide poisoning. *A*, shadow cells in the cortex. The cells are faintly outlined and stain poorly (dog 171). *B*, high power study of cortical ganglion cells, showing the frayed and vacuolated cytoplasm (dog 264). *C*, frayed and vacuolated cells in the paraventricular nucleus (dog 290).

changes were observed. The astrocytes and oligodendroglia were most affected; the microglia showed few changes. The astrocytes were swollen and sometimes ameboid; the oligondendrocytes showed evidence of acute swelling.

The small cortical vessels were diseased in all cases. As a rule the arterioles of the upper cortical layers, especially the lamina zonalis, were most affected, but the arterioles elsewhere in the cortex were also damaged. The change consisted of thickening of the arteriolar wall, a

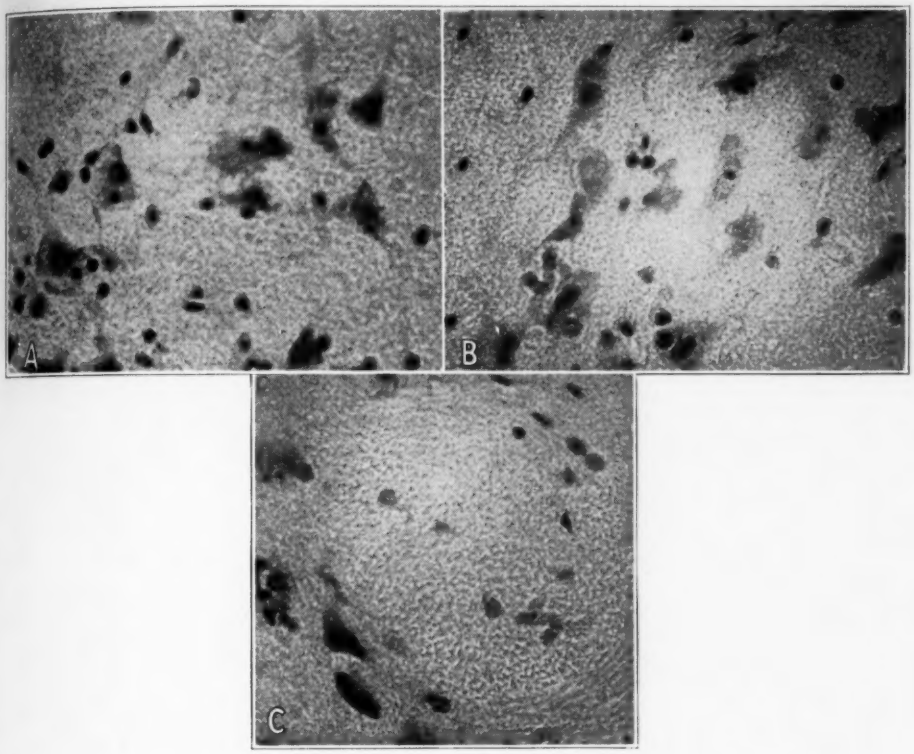

Fig. 3.—Changes in the basal ganglia in experimental carbon disulfide poisoning. *A*, distorted and frayed large ganglion cells in the caudate nucleus (dog 290). *B*, changes similar to those shown in *A* (dog 264). *C*, degenerative changes in cells of the pallidum.

hyaline-like appearance of the wall and frequently proliferation of the endothelial lining of the vessel. The last change was not present in every case, but it was sufficiently frequent to be regarded as part of the disease process. The vascular changes were as constant as those of the ganglion cells, but were not as pronounced.

The structure of the myelin sheaths was normal.

Basal Ganglia: The striatum (caudate nucleus and putamen) was damaged in all cases. The degree of damage paralleled the cortical disease closely. The large and small ganglion cells were equally affected, the small cells being probably the more severely diseased. The type of change in the ganglion cells was exactly the same as that in the cortex. Vascular changes similar to those in the cortex were not usually seen. Just as in the cortex, there was no proliferative glial response.

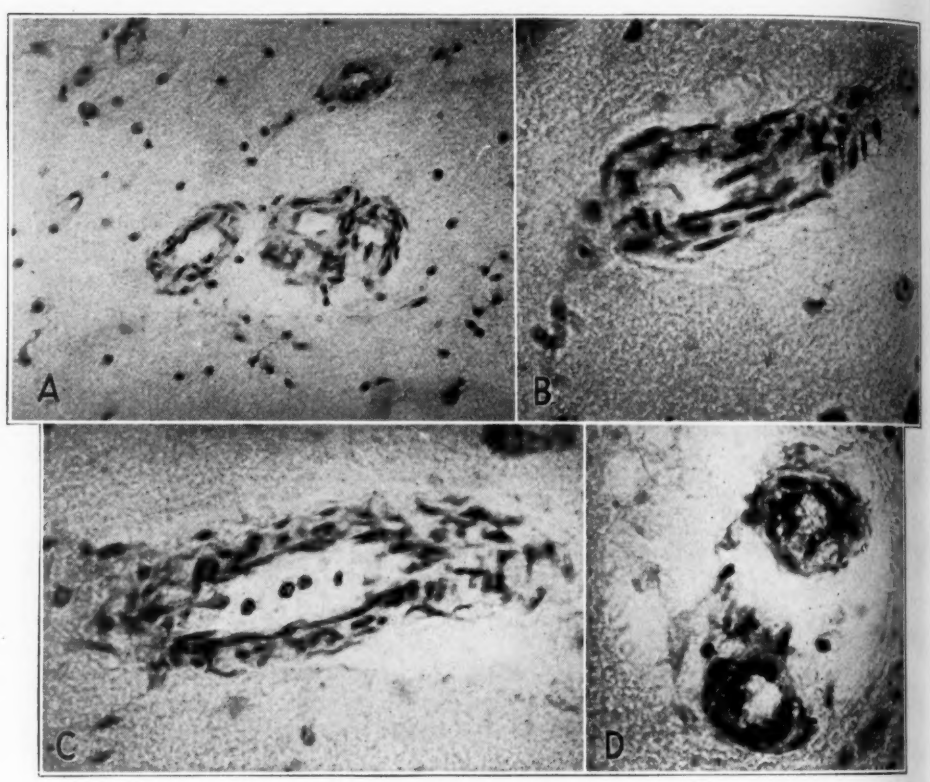

Fig. 4.—Vascular changes in experimental carbon disulfide poisoning. *A*, a large vessel with proliferated walls and two adjacent thickened arterioles in the cortex (dog 264). *B*, a thickened cortical vessel showing the proliferative changes in the wall of the vessel (dog 171). *C*, a similar process in another cortical vessel. *D*, thickened and hyalinized arterioles in the caudate nucleus (dog 290).

The pallidum was much less severely damaged than the striatum; only scattered cell changes were seen. The same was true of the nucleus ruber.

Cerebellum: The Purkinje cells were diseased in all cases. There was wide variation, however, in the degree of damage to these cells, it being more severe in some instances than in others. In no instance

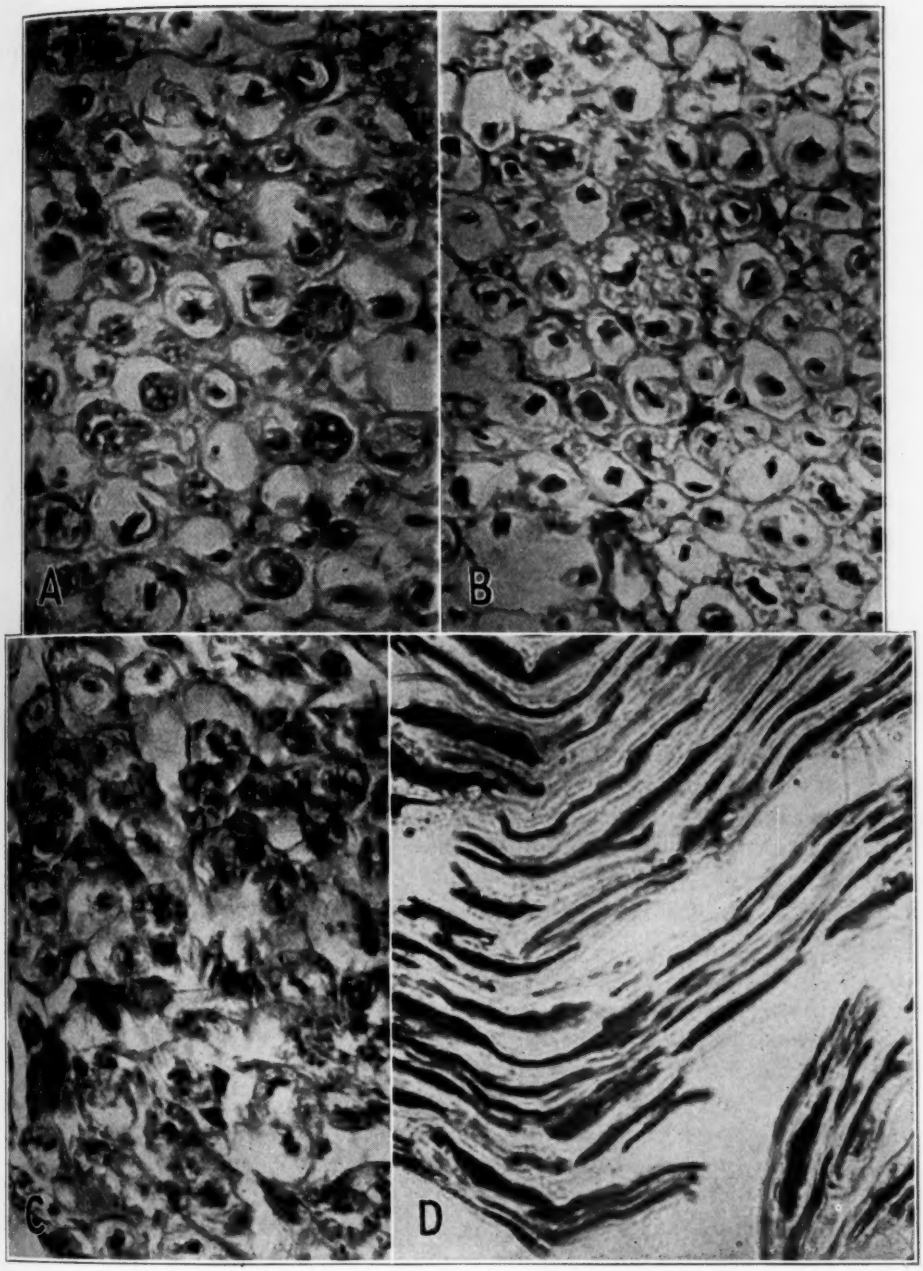

Fig. 5.—Changes in the nerves and nerve roots in experimental carbon disulfide poisoning. *A*, loss of myelin and swollen and fragmented myelin sheaths in the sciatic nerve. The axis-cylinders are swollen. *B*, a change similar to that shown in *A*, of less pronounced degree. *C*, almost complete loss of myelin in a posterior root, with great distortion of the axis-cylinders. *D*, axis-cylinders from the sciatic nerve showing distortion, swelling and fragmentation (Bodian stain).

were all the Purkinje cells affected; there were always cells which appeared normal, though the number of diseased units varied considerably from case to case.

The characteristic change consisted of swelling of the cytoplasm, with loss or pulverization of the Nissl substance. The nucleus was likewise swollen and the nuclear membrane often distinct.

The granule cells were not diseased. Some of the cells in the molecular layer showed evidence of disease in some cases.

Brain Stem: There were few changes in the ganglion cells of the brain stem, despite the widespread damage to the cerebral cortex and parts of the basal ganglia. The nuclei of the cranial nerves were all normal. No evidence of disease was seen, either in cell or myelin sheath stains, in the diencephalon, mesencephalon, pons or medulla.

Spinal Cord: The changes in the spinal cord were not striking. No changes of significance were disclosed in the white matter except for mild evidences of edema in a few animals. The vessels within the anterior and posterior horns were congested. This was particularly noticeable in the anterior horns, in which punctate hemorrhages were also seen in a few cases. The anterior horn cells were moderately well preserved. Here and there one could see a decrease in their numbers, but in general there was no striking loss of cells. Only moderate evidences of disease were observed in scattered cells. The nucleus was sometimes swollen, the nuclear membrane destroyed, the entire nucleus strikingly pale and the nucleolus greatly swollen. In such cells the cytoplasm gave no evidence of changes. Some anterior horn cells were swollen and had tortuous dendrites; others were shrunken. The meninges and the anterior and posterior roots showed no changes.

Peripheral Nerves: The brachial plexus and the sciatic nerve were examined in all the animals. Cell stains revealed swelling and fragmentation of the myelin sheaths. This had not progressed to the stage of complete demyelination, for sections stained for myelin sheaths invariably appeared normal. Bodian stains of the peripheral nerves showed swelling and fragmentation of the axis-cylinders. The axons were often swollen far beyond their normal size. It seems clear, therefore, that the changes in the peripheral nerves affected primarily the axis-cylinders, and to a lesser degree the myelin sheaths.

COMMENT

The problems of greatest importance in carbon disulfide poisoning may be stated thus: (1) What are the changes found in this disease, and (2) may they be regarded as characteristic? The latter is, of course, of first importance from the practical point of view, but before this can be answered it is desirable to determine the changes in the nervous system in cases of carbon disulfide poisoning.

Neither the changes in man nor those in experimental animals can be regarded as pathognomonic or characteristic. The changes in the cases of carbon disulfide poisoning in man are variable. They are similar to those observed in animals in three respects: the alterations in ganglion cells, the damage to vessels and the changes in peripheral nerves. The changes in the ganglion cells of the cerebral cortex are similar to those observed in the experimental animal, but they are less severe and less extensive. This may be due to the fact that animals are subjected to a more concentrated dose of the gas than are human beings and, further, that the exposure of persons to the gas is more prolonged, chronic and sublethal than that of animals. This probably accounts for the more chronic type of cell change observed in the human brain. Interspersed among the chronic cell changes, however, are acute or subacute cell alterations similar to those seen in animals. In both man and animals, moreover, there is extensive damage to the basal ganglion system, particularly the striatum and to a lesser degree the pallidum. Many persons with carbon disulfide poisoning show more or less complete evidence of parkinsonism, which can be attributed to changes in the extrapyramidal system.

Of particular interest is the damage to Purkinje cells, both in man and in animals. This is more extensive in the latter, but it is found also in most of the cases of poisoning in man. It accounts probably for the severe ataxia observed in the dogs described in these experiments. There is no evidence of the cerebellar tract system to explain the severe ataxia observed in all the experimental animals.

One point in common in animals and man is the evidence of vascular disease. This has been observed in practically all the human material studied at autopsy, and constitutes a feature which is even more striking than the changes in the ganglion cells. In both the changes in the vessels consist of proliferation of the vascular endothelium and thickening and hyalinization of the cortical arterioles. The larger pial vessels are not affected. The matter is of some importance, for in cases of poisoning in man the problem arises as to whether the changes in the vessels constitute a feature of carbon disulfide poisoning or whether they must be regarded as having no connection with the disease process. No definite answer is possible on the basis of the changes in animals.

There is no question that extensive damage is observed in the brain in cases of experimental carbon disulfide poisoning, and that this damage is present to a lesser degree in man. There is injury also of the peripheral nerves, more pronounced in man than in experimental animals. The spinal cord shows only minor degrees of damage. The type of change, however, is nonspecific. It is not possible from the histologic observations alone to make a diagnosis of carbon disulfide intoxication, without knowledge of exposure to the chemical. The degenerative

changes in the cerebral ganglion cells, striatum, Purkinje cells and peripheral nerves are capable of production by any one of many chemical substances; hence the extensive damage observed, especially in experimental animals, cannot be regarded as a specific manifestation of carbon disulfide poisoning. It is merely the expression of severe damage by a poison which appears to have a close affinity for the nervous system.

SUMMARY

This study includes a survey of the changes in the nervous system in man and in experimental animals following carbon disulfide poisoning. A comparison of the two discloses the fact that in the human nervous system one finds scattered changes in the ganglion cells of the cerebral cortex of varying degree, depending on the severity of the intoxication, disease of the basal ganglia and peripheral nerves, and evidence of vascular involvement; in the experimental animal there are more extensive damage to the cerebral cortex and basal ganglia, injury of the Purkinje cells, vascular changes, minor damage to the spinal cord and involvement of the peripheral nerves. The changes in the ganglion cells are nonspecific and are merely a manifestation of injury by a noxious agent. The difference in the changes in man and in the experimental animal may be explained, in part at any rate, by the difference in length and degree of exposure to the chemical.

ABSTRACT OF DISCUSSION

DR. S. T. GORDY, Philadelphia: The loci of injury to the central nervous system in man and in experimental animals, with minor exceptions, are essentially the same, although they may vary in intensity. The findings in the experimental animals are striking—not only the neurologic signs, such as the tremors, ataxia, myoclonic movements and muscular atrophies, but also the evidences of encephalopathy, the changes in personality, apathy, surliness and apprehensiveness.

Of further interest in the autopsy observations on human material studied by the authors was that, despite the factors other than carbon disulfide poisoning which apparently complicated the clinical picture, characteristic toxic disease of the cerebral ganglion cells, peripheral neuropathy (neuritis) and arteriosclerosis of the cerebral vessels occurred. The authors are unduly reticent in referring to these changes as nonspecific. Their persistence connotes a high degree of specificity, in the sense that they constitute a definitive pathologic syndrome: a triad of ganglion cell disease, peripheral neuropathy and cerebral arteriosclerosis.

I should like to ask whether any pathologic studies of the animals were made other than those of the nervous system. Many of the patients whom I have observed displayed extraneurologic syndromes—gastrointestinal, vasomotor and respiratory—which were frequently as striking as the neurologic symptoms. Dr. Lewy has also seen patients with loss of libido and potentia, and there have been reports of cases in which the adrenal glands were destroyed. Some of these extraneurologic symptoms may precede by a long period the neurologic symptoms which incapacitate the patient. There may first be respiratory symptoms which

mimic closely pulmonary tuberculosis or asthma. Such a picture frequently misleads the clinician and draws his attention away from the nervous system. Subsequently the manifestations of encephalopathy and peripheral neuropathy emerge.

One would like to speculate on the direct cause of the neuropathologic changes. It is often said they are anoxic in origin. I believe one should be reticent in saying that a condition is specifically anoxic, but anoxia may have indirect significance here. This hypothesis arises from the newer work with vitamins, which has shown their intermediate importance in neural metabolism, especially the utilization of oxygen. Do carbon disulfide and similar toxic agents (fat solvents) have a depressive effect on the enzymes of the central nervous system, especially those which mediate the utilization of oxygen, the dehydrogenases, for instance? This may be the explanation of the changes in the central nervous system.

Dr. Armando Ferraro, New York: I am glad to be in a position to confirm in general the observations that Dr. Alpers and Dr. Lewy have presented concerning the pathologic picture of carbon disulfide poisoning. My associates and I at the Neurological Institute have material on the experimental intoxication caused by carbon disulfide. We have used cats and rabbits, however, instead of dogs. We found that the pathologic changes are diffused through the cortex, the basal ganglia and the cerebellum. In the early stages they consist mainly of swelling and diminution of nerve cells. I think that in the acute stage the process is reversible and that recovery may take place if the animal is not further exposed to the gas.

Later, when the lesions were more severe, we have observed small, diffuse, minute softenings in the cortex. In 1 instance we noted softening also in the globus pallidus. We did not find softening constantly predominant in the striatum. In addition, we have constantly seen, in 7 of 8 cats, bilateral softening of the dentate nucleus. It is the most striking pathologic change in our series, and it applies only to cats. We did not see this softening of the dentate nucleus in rabbits; the presence of the lesion in cats raises again the important issue that one should take into consideration the type of animal with which one is working; along with experimental pathology a new field is gradually developing, that of comparative pathology.

The presence of softening in the dentate nucleus may explain some of the cerebellar symptoms that have been reported by Dr. Alpers and Dr. Lewy and the experimental lesions of the dentate nucleus already reported by Dr. Fulton and his colleagues in Macacus rhesus monkeys.

We have failed to find any structural pathologic changes in the blood vessels, but this, again, may be due to the fact that we used cats, in which there may exist better resistance of the blood vessels than in dogs. Supporting the contention is the fact that in lead poisoning I have been unable to reproduce experimentally that characteristic involvement of the blood vessels which has been reported in man, and other authors have failed to reproduce in cats subjected to experimental intoxication with insulin characteristic vascular changes reported in dogs.

With regard to the pathogenesis of lesions in carbon disulfide poisoning, in view of the fact that we have failed to find any important vascular change, I am inclined to accept from the experimental standpoint the explanation that probably there has been interference with oxidizing enzymes and that therefore the action of carbon disulfide may be compared with that of narcotics, such as ether and chloroform.

Dr. Philip Drinker, Boston: I am not a physician, and I do not wish to make any criticism of the pathologic picture in the light in which it has been presented. Dr. Lewy was at some pains to state that concentrations which he used in his experimental studies were of the order of 400 parts per million, and to point out that roughly this is one hundred times as high as that found industrially. This is an implied compliment to industry. I am not sure that industry has quite achieved that good a result, but it is certainly on the way to it.

The other discussers have not been specific as to the concentrations which they have been using. In our work with experimental inhalations, in which we ourselves were the subjects, my colleagues and I have been dealing with concentrations ranging from about 5 to 50 parts per million. We have followed the rate at which carbon disulfide is excreted in urine, and we intend to do the same with blood.

It seems to me that one of the most significant contributions to the pharmacology of anesthetics was that made by Haggard some years ago in experiments with ethyl oxide, in which he exposed animals to known concentrations and followed the rate at which the substance was excreted. As a corollary, he determined in admirable fashion the physicochemical and biochemical principles of distribution of the gas between body fluids and water. We are embarking on just such a research for carbon disulfide, but we shall deal only with the concentrations which we now think are industrially significant, namely, those below 25 or 30 parts per million. The usual concentrations are below 10 parts per million; those with which we shall deal will cover that range, possibly up to about 50 parts per million. This work will be done on animals, and when we have perfected our technic as we hope to do, the investigation will be followed up on human subjects. As the result of this study, we hope to show how rapidly saturation of any body fluid is attained with carbon disulfide in any concentration and how rapidly desaturation of the blood occurs.

Dr. Noble R. Chambers, Syracuse, N. Y.: I should like to ask what are the principal sources of carbon disulfide poisoning in industry.

Dr. Bernard J. Alpers, Philadelphia: I cannot discuss the clinical features of carbon disulfide poisoning because I have had no experience in examining patients exposed to that chemical. I shall confine my remarks to the questions raised by Dr. Gordy, who emphasized the specificity of the changes. It is important to stress the fact that both in man and in animals it is impossible to say from a picture seen under the microscope that there has been exposure to carbon disulfide.

It seems to me that too much is explained on the basis of anoxia. So far as I know, though I may be wrong, there is no physiologic evidence that carbon disulfide acts as an anoxic agent. Just what the mechanism of the production of these changes is remains to be determined.

In answer to Dr. Ferraro's question, I was unable to observe any changes in the dentate nucleus.

I am not competent to discuss Dr. Drinker's comments except to say it should be emphasized that these experimental concentrations are greater than those to which industrial workers are exposed; it is important, however, to determine in animals just what might occur in the central nervous system when there is a high concentration of the chemical.

It is possible that too much emphasis has been placed on changes in the central nervous system in these cases and that more should be placed on those in the

peripheral nerves. However, the changes in the peripheral nervous system are variable. They seem to be more marked in man than in animals. I cannot explain that except to suggest that possibly a longer exposure to minimal concentrations may have some effect on man.

DR. F. H. LEWY, Philadelphia: In reply to Dr. Gordon's question, I wish to state that no carbon disulfide was recovered from any animal organ and that the adrenal glands showed no pathologic changes.

The rubber industry was for many years the principal source of carbon disulfide poisoning, until "hot vulcanizing" was generally introduced. At present this hazard is mainly found in the viscose rayon industry, in the olive oil–extracting and chemical-cleaning industries and in odd repair jobs, such as that of golf ball–repairing.

SURGICAL DIVISION OF COMMISSURAL PATHWAYS IN THE CORPUS CALLOSUM

RELATION TO SPREAD OF AN EPILEPTIC ATTACK

WILLIAM P. VAN WAGENEN, M.D.
ROCHESTER, N. Y.
AND
R. YORKE HERREN, M.D., PH.D.
PORTLAND, ORE.

The theory has long been held that the disordered wave of nerve impulses resulting in an epileptic seizure with loss of consciousness usually begins at one focal point and then spreads widely to other parts of the neopallial portion of the brain. When the spread is local, only local manifestations are experienced, such as flashes of light, hallucinations of sound, movement of muscles characterizing a "jacksonian attack," sensations of taste or smell and sensory changes, such as tingling and paresthesias. In instances in which the disordered spread of impulses is still wider, consciousness may be lost, tonic and clonic movements of both sides of the body may take place, sphincter control may be lost and various vasomotor changes be experienced and observed. As a rule, consciousness is not lost when the spread of the epileptic wave is not great or when it is limited to one cerebral cortex.

The theory that the foci from which epileptic waves are supposed to originate should be removed has long been held and practiced. Tumors have been removed, scars excised, fragments of bone impinging on the cortex elevated and silent areas of brain, often normal in gross appearance, extirpated in the effort to remove an irritable focus, or the "firing point," for epileptic waves. All too often has a multiplicity of firing points been found. No sooner has one been dealt with surgically than another has assumed control. All too frequently has the firing point been inaccessible or in such an area that its removal would lead to serious palsy or disturbances of important functions, such as speech.

A series of observations led to the belief that an epileptic wave could be confined to one hemisphere of the brain. During such an attack consciousness was not lost and generalized convulsive movements did not occur. Sphincter control was maintained, and the mental and physical hazard of an epileptic attack was largely averted.

From the Department of Surgery, Division of Neurosurgery, the University of Rochester School of Medicine and Dentistry, and Strong Memorial Hospital, Rochester, N. Y.

The first observation was made in a study of our series of tumors (gliomas) of the corpus callosum. Almost all these tumors are to be classified as glioblastomas, the life history of which is from twelve to fifteen months. In the early part of the life history of the tumors in this series convulsions were common. In late stages convulsions were much rarer; if they did occur they were unilateral and usually were not accompanied by loss of consciousness. In other words, as the corpus callosum was destroyed generalized convulsive seizures became less frequent.

The second observation was made in a study of a patient who had been committed to the Rochester State Hospital and was seen after a self-inflicted injury to the head. Neurologic examination and roentgenograms gave evidence of multiple tumors of the brain. At operation many meningiomas were encountered over the cortex of each hemisphere, with one large tumor in the right frontal region. After the removal of numerous small surface tumors, from 1 to 4 cm. in diameter, and of the large meningioma, another nodule of tumor was seen arising from the inferior margin of the falx in its midportion and projecting into the substance of the corpus callosum. This tumor measured about 4 cm. in diameter after removal. The history in the case included many convulsive seizures in the early stages of the disease and few in the late stages. It was inferred that convulsions became less frequent as association pathways were destroyed.

The third observation was made in a postmortem study of the brain of a person who had had frequent epileptic attacks for about twenty-five years. After a cerebrovascular accident, five years prior to death, the epileptic attacks ceased. Autopsy showed that the fibers making up nearly two thirds of the body of the corpus callosum and the upper part of the genu were interrupted by the scar of a former hemorrhage from the anterior cerebral artery.

A fourth observation concerned a person who had suffered a cerebral hemorrhage, presumably from a branch of the middle cerebral artery in the sylvian fissure. The patient gave a history of epileptic seizures for about twenty-five years. The right side of the brain was affected by the hemorrhage. The patient was right handed. After this vascular accident the patient became hemiplegic but the epileptic seizures ceased. It was inferred that the focus for attacks had been destroyed by the hemorrhage or by the softening of the brain accompanying it.

With these clinical observations in mind, it was decided to divide the corpus callosum surgically in an effort to limit the spread of a convulsive wave to one half of the cerebrum. This structure has always been looked on as hallowed ground. Innumerable functions have been ascribed to it. Lesions of the corpus callosum in the anterior half have

been said to result in apraxia, astereognosis, incontinence of feces and urine, Korsakoff's syndrome and marked mental changes, such as disturbances of memory, reason, association of ideas and motor coordination. Writers have been less definite and less convinced concerning functions of the splenium, since it has been divided several times in approaches to the third ventricle. Certain disturbances of the visual fields resulting from division of the splenium have been postulated but never proved. It should be stated that most of the assumptions concerning the function of the corpus callosum have been based on the study of tumors involving it which also injured both frontal lobes or both frontoparietal regions. The disturbances in function are almost certainly the result of disturbance in function of the frontal or parietal lobe, and not of the corpus callosum per se.

An adequate and justifiable opportunity to section the corpus callosum first presented itself on Feb. 6, 1939.

METHOD

Preoperative Study.—In the cases to be reported the preoperative study consisted of the usual general, neurologic and laboratory examinations to rule out tumor of the brain, hypoglycemia, syphilis and similar conditions as a background for attacks. Plain roentgenograms of the skull were taken routinely. Encephalograms were made when the history suggested the possibility of a single cerebral scar. Electroencephalograms were obtained routinely. Photographs or motion pictures were taken when there were abnormalities of gait or posture or palsy of any extremities. An electrobasographic record of gait was obtained. Detailed studies were made by a psychiatrist and a psychologist. On some patients studies of gastric motility were made for a comparison with the postoperative state.

Postoperative Study.—The postoperative study was a repetition of the foregoing procedures with omission of plain roentgenograms of the skull and encephalograms. Particular attention was paid to the postoperative psychiatric and psychologic examinations. Every attempt was made to secure monthly reports of the patients' activity and general condition.

REPORT OF CASES

CASE 1.—*Birth injury, probably thrombosis of the left middle cerebral artery, followed by a large porencephalic cyst in the parietal and temporal lobes; convulsive seizures for ten years. Partial division of fibers of the corpus callosum.*

History.—G. R., a man aged 33, single, entered the hospital on Feb. 6. 1939, because of convulsive seizures, of ten years' duration. Apparently he had suffered a birth injury to the left cerebral hemisphere, which manifested itself by withering and spasticity of the right arm and leg. In spite of the cerebral injury, his mentality was average, and his college education was interrupted after two years for financial reasons only. Since then he had worked at various jobs, the last being that of a foreman for the Works Progress Administration.

Ten years before his admission to the hospital he experienced the first generalized convulsion. This came on without aura and lasted from ten to fifteen minutes. Since then he had had four, five or six attacks a year. He had had three

attacks within the last four months. At some times an aura, consisting of a sensation of "being under terrific tension," occurred for a few moments before the attacks. At other times the attack was preceded by dizziness, followed by a sensation of "floating in air." Sphincter control was not lost during the seizure. Palsy after the attack was of no greater degree than before it. The patient was not certain that the convulsion started in the withered arm. In addition to the major convulsive seizures he experienced many transient episodes of vertigo and momentary confusion. In spite of the almost continuous use of phenobarbital for ten years, the attacks had been increasing in number.

Examination.—The patient was bright, alert and agreeable, with apparently good insight into his trouble. His memory was excellent. His ability to reason and argue was normal. Speech was slow and deliberate, and he gave the impression of weighing his words. When he was hurried he had a slight tendency to stutter.

General physical examination disclosed no abnormality. Neurologic examination revealed: (1) withering and shortening of the right arm and leg, the scars of former operations for correction of contraction deformity of the wrist and ankle being visible; (2) increase in deep reflexes on the right side; (3) hypesthesia for all forms of sensation on the right side; (4) a right lower quadrant visual field defect, and (5) associated movements of the right or affected hand when the left hand was moved either actively or passively. The last-mentioned finding was constant. Associated movements of the toes of the right foot were noted on one occasion when active movements of the toes of the left foot were slowly carried out. Laboratory data, including the roentgenographic appearance of the skull, were normal. An electroencephalogram showed predominance of abnormal waves in the left frontoparietal and temporal regions.

Operation.—On Feb. 11, 1939, a left osteoplastic bone flap was made, the incision in the bone being carried about 1 inch (2.5 cm.) across the midline to expose the superior longitudinal sinus from the midfrontal region to the junction of the middle and the posterior parietal region. Anesthesia was induced by avertin with amylene hydrate (70 mg. per kilogram of body weight), 1 per cent procaine and ether. A large porencephalic cyst was encountered in the left midparietal and temporal regions. The gyri of the middle and superior portions of the temporal lobe were absent anteriorly. The left hemisphere was retracted laterally and the corpus callosum exposed. The fibers were divided from the middle region of the genu to a point in the anterior third of the splenium. The ependyma of the lateral and third ventricles was seen after this division, and the third ventricle was opened at one point. The bone flap was replaced in such a way as to bring the dura out of the wound between the edges of the flap instead of resuturing it.

Postoperative Course.—The patient's course after operation was satisfactory. Consciousness was regained in the usual time. No untoward effects of the operation could be seen. Speech, memory and general mental habit were unchanged. Gait and movements of the right shoulder girdle were unaltered.

Three days after operation the patient experienced four jacksonian seizures. In three of these the right arm only was involved; in the fourth the arm and face were affected. Consciousness was not lost. Speech could be carried on normally during these attacks, which lasted from ten to thirty seconds. The next day two more jacksonian seizures were observed, again without any impairment of consciousness.

The associated movements of the right, or affected hand, when the left hand was moved either actively or passively, persisted, in spite of the division of the

fibers of the corpus callosum. The patient was reexamined two months after operation, and the same phenomena were noted. The most likely explanation of this seems to be bilateral representation of the arm and hand in the cortex of the right hemisphere.

CASE 2.—*Trauma to the head without loss of consciousness in 1928; onset of convulsions five months later, which have persisted to date. Partial section of the corpus callosum; recurrence of convulsions; complete section of the corpus callosum.*

History.—In 1928 W. S., a farmer aged 26, single, fell from a boxcar and struck the occipital region of the skull. He was dazed but did not lose consciousness. Five months later he experienced the first generalized convulsion, which came on without warning. Attacks persisted until the date of admission. The only lateralizing feature was nystagmus to the right, observed in one attack. Seizures varied in frequency from one a day to one every ten to twelve months. Just prior to admission to the hospital they occurred nearly every week. Neither the administration of phenobarbital nor dehydration made any difference in the frequency.

Examination.—The patient was husky and appeared normal. He was alert, keen and quick, but was shy in the new environment. His schooling had been limited to the elementary grades. Neurologic examination showed nothing abnormal except horizontal nystagmus on one occasion.

All laboratory data were normal, including those on the spinal fluid. An encephalogram showed slight evidence of atrophy of the frontal lobes. An electroencephalogram was noncontributory to the localization of a single focus for abnormal discharges. Abnormal waves from many areas were recorded before the first as well as the second stage of operation.

Operation.—On Feb. 22, 1939, partial section of the corpus callosum was made. In exposing this structure three veins from the frontoparietal lobe was ligated. Approximately 5 cm. of the midportion of the corpus callosum was divided. A clip was placed on the posterior end of the fiber incision.

Postoperative Course.—The immediate postoperative course was marked by weakness of the left arm and leg, which, however, returned nearly to normal by the time the patient left the hospital.

Postoperative Seizures: The first seizure occurred about two hours after operation and was noted to begin on the right side. Six hours after operation another seizure, beginning on the left side, was observed. The eyes were turned toward the left. Consciousness was lost. During the first twenty-four hours after operation seven more convulsions occurred. All were on the left side. Five days after operation, there was another series of convulsions on the left side, without loss of consciousness.

Second Operation.—On Feb. 27, 1939, the bone flap was reelevated under procaine anesthesia, because a subdural hematoma was suspected. Accumulation of subdural fluid was minimal. One of the larger veins which had been ligated when the corpus callosum was exposed had become thrombosed laterad well into the arm area. The corpus callosum was reexposed and another portion of 1.5 cm. divided in the region of the genu.

Postoperative Course.—The patient had no more seizures during his stay in the hospital. He was discharged on the fortieth day after admission. Detailed psychologic and psychometric studies, which will be reported in another communication, were carried out during the postoperative course. It is sufficient to state that the patient did not show any evidence of loss of memory, change in personality, aphasia, apraxia or astereognosis. During his stay in the hospital he

became friendly with other patients and lost his country shyness and his blank expression. As evidence of his mental alertness it may be noted that he soon became the champion pinochle player of the ward.

Second Admission.—Approximately one month after his discharge from the hospital he experienced a series of convulsions, some with loss of consciousness and some without. Part of these were mainly on the left side and part were generalized. No aura was noted.

Third Operation.—On May 4, 1939, the wound was reopened. The corpus callosum was reexposed and divided from the rostrum to the tip of the splenium. The fornix was also divided in two places, first, immediately anterior to the foramen of Monro and, second, just where the fornix joins the body of the corpus callosum. The postoperative course was uneventful. Again, at the time of writing, the patient shows no untoward mental changes and no evidence of apraxia or astereognosis.

CASE 3.—*Birth injury; convulsions since the age of 2 years. Partial division of corpus callosum; return of convulsions; complete division of the corpus callosum and left limb of the fornix.*

History.—F. R., a woman aged 26, was born after a difficult labor. The left collar bone and "shoulder bone" were broken. There was a "deep tear" over the left eye. Convulsions started at the age of 2 years and continued intermittently until the time of her admission to the hospital. At the age of 17 years iritis developed. The Wassermann reaction of the blood was positive. The spinal fluid was normal. The Wassermann reaction of the blood became normal after treatment and remained so. The father had a positive Wassermann reaction. The convulsive disorders were not altered to any degree by antisyphilitic treatment.

The convulsions occurred at varying frequencies, from one a year to several a week. An aura was never noted, and a history of localization of origin of the attack could not be gained. The convulsive movements were about equal on the two sides. Incontinence usually occurred, as well as tongue biting. The patient was keenly aware of her handicaps, and realized that the convulsions were responsible for curtailment of her education and almost total segregation from society. There were few, if any, of the usual evidences of mental deterioration that may occur after years of seizures.

Examination.—The patient was short and stout, with partial palsy of the muscles of the left shoulder girdle and a contracture at the left elbow. Neurologic examination gave normal results except for absence of deep reflexes in the left arm and variable nystagmus. All laboratory data were within normal limits, including those for the spinal fluid. An encephalogram in 1937 (November) failed to give evidence of cerebral atrophy or scar. An electroencephalogram in February 1939 showed abnormal waves from many areas. No conclusion was reached as to the presence of a single dominant "firing point."

Operation.—On Feb. 23, 1939, the body and upper half of the genu of the corpus callosum were divided.

Postoperative Course.—The patient made a slower return to the preoperative state than did others, and it was not until the second postoperative day that she began to initiate speech and take much interest in her surroundings. Speech was often repetitious, and she was apt to refer to herself in the third person, saying, for instance, "R. has a headache." This phenomenon, however, disappeared entirely in about a week.

Four days after the operation the patient had a convulsion on the left side without loss of consciousness. She was able to describe some of the events of the seizure and later to describe a similar attack occurring on the right side. At the time of her discharge from the hospital she seemed to have returned essentially to her preoperative state, both mentally and physically. After discharge from the hospital she had a series of generalized fits with loss of consciousness, similar to those of the preoperative state.

Second Operation.—On May 25, 1939, the wound was reopened and the entire corpus callosum and the left limb of the fornix were divided. The patient made an uneventful recovery and was discharged on the eighteenth day. Physical, psychiatric and psychologic examinations gave results that were essentially the same as those recorded before operation. No further convulsions have occurred to date.

CASE 4.—*Convulsions since the age of 1½ years; injury of the brain and of the brachial plexus at birth. Partial division of the corpus callosum.*

History.—R. M., a boy aged 10 who was admitted from Craig Colony to the outpatient clinic of Strong Memorial Hospital had had various complaints for nine years. The birth record was that of a difficult delivery after intermittent labor for ten days. Injury to the right brachial plexus was noted soon after birth. The head was "bashed in" by forceps, according to the mother. The patient's development was good and essentially normal until he was 18 months of age, when he had a generalized convulsion, the first of a series which persisted until his admission to the clinic. At times the patient was in status epilepticus and needed general anesthesia for relief. The pattern of the seizures varied slightly from time to time, but were essentially of the generalized type that involves all extremities alike. The convulsions came without aura, lasted from a few moments to several hours and were followed by sleep. Vomiting might occur several hours before an attack. Fever seemed to precipitate a series of convulsions as readily as anything. In 1935 the boy was struck by an automobile and rendered unconscious. The record of convulsions remained unchanged. In the same year simple right mastoidectomy was performed. In 1937 the patient was sent to Craig Colony because of continued severe attacks and remained there for the greater part of the time until his admission to this hospital, in February 1939.

Examination.—The patient was moderately well developed. He was shy and talked to one only after several days' acquaintance. However, he seemed bright and was quick at play. He read children's books, and his ability to reason and calculate was moderately good for his age. His ability to clothe himself, play and carry on other activities was limited by an injury to the right brachial plexus, involving the lower portion of the arm, and left hemiparesis affecting mainly the arm. Examination of the visual fields showed a left homonymous hemianopia with constriction of the remaining fields. Visual acuity, however, was normal. An electroencephalogram gave evidence of greatest abnormality in the upper part of the right motor area. There was to be noted the same phenomenon as in case 1—involuntary associated movements of the left hand whenever the right hand was opened or closed, voluntarily or involuntarily. This was not noted in the foot or toes.

Operation.—On March 4, 1939, the body of the corpus callosum was divided, the greater part of the genu and splenium being left intact.

Postoperative Course.—Recovery was exceptionally smooth and uneventful except for recurrence of bed wetting at night for the first three weeks after

operation. This has largely disappeared since discharge from the hospital. The only hint of a convulsive disorder is found in the mother's observation that although the boy had been well since going home, he had had a headache on April 24, had wet the bed during the night and had vomited. The child was not certain that he had had a seizure.

The patient's mental condition is at least as good as before operation. The parents are insistent in their claims of improvement in mental function, as well as in general deportment and habits, such as eating and bowel movements. The associated movements of the left, or spastic, side when the right is moved have persisted since division of the corpus callosum.

CASE 5.—*History of convulsions since the age of 9; gradual mental deterioration. Partial section of the corpus callosum; recurrence of attacks. Complete section of the corpus callosum.*

History.—E. J. B., a single woman aged 24, who was on parole from the Rochester State Hospital, had been considered well until the age 9, when the first of a large number of convulsive seizures occurred. She was able to complete three years of high school before the number and severity of attacks and mental deterioration prevented further schooling. The attack was usually preceded by a day or two of nervousness and a feeling of tension, and at times of vertigo. Nothing in the history suggested localization of the attacks. Between spells the patient might be quiet, tractable and despondent, or aggressive, profane, abusive and quarrelsome. She was observed to be ambidextrous, but was more right handed than left handed.

Examination.—The patient was slim and lean, with mouselike features. The skin was pitted from old and recent acne. General physical examination gave normal results except for a chronic infection of the middle ear. Results of neurologic examination were entirely negative. All laboratory data were normal. Mentally the patient showed evidences of deterioration. She was interested in the care of long finger nails, but not in that of her hair or dress. She was confused and at times irritable, and made feeble attempts at being coy. Pictorial magazines interested her, but little else in reading material. An electroencephalogram showed abnormal waves from many areas, but more from the left frontal lobe than elsewhere.

Operation.—On March 18, 1939, the corpus callosum was exposed under anesthesia induced by procaine, ether and avertin with amylene hydrate. The upper half of the genu and the body were sectioned. The longitudinal sinus was ligated in the anterior portion. No veins of consequence were ligated in gaining exposure.

Postoperative Course.—The course after operation was surprisingly smooth and uneventful. There was no evidence of aphasia or apraxia. In a few days the mental responses were better than at any time while the patient was under observation; she seemed to be able to make better use of her faculties than previously. Twelve days after operation she had two seizures, with loss of consciousness and sphincter control. A second electroencephalogram showed predominance of abnormal waves from the right occipital region, whereas the greatest disturbance previously had been in the left frontal region.

Second Operation.—On April 24, 1939, the corpus callosum was reexposed and sectioned from the rostrum to the tip of the splenium.

Postoperative Course.—The immediate course was uneventful. Forty-eight hours after operation, at 3 a. m., the patient was heard to give a cry. The nurse

found her sitting up in bed and breathing rapidly. The pupils were dilated, and she appeared apprehensive. Consciousness was intact. The next day, at 4 a. m., the same thing occurred. The attacks appeared to conform in a measure to those described of diencephalic origin. The patient was given carbohydrate feedings at frequent intervals. A few days later a generalized convulsion occurred, with loss of consciousness. The value for blood sugar was recorded as 70 mg. per hundred cubic centimeters. No further seizures have occurred. Mentally, the patient is at least as intact as on admission, and the mother is impressed by her greater composure and tractability. There are no abnormal neurologic findings.

CASE 6.—*Convulsions since the age of 12, without aura, partial division of the corpus callosum.*

History.—H. K., a girl aged 16, had a single convulsion of unknown origin, in infancy. At the age of 5 she fell and "struck her head." The details of the accident are not known. Immediately afterward she had a generalized convulsion, with biting of the tongue and incontinence. At the age of 12 another attack occurred, and she has since had from two to thirty a year. During the two weeks before admission a series of five seizures occurred; they were without aura or lateralization. The patient had always been bright and alert, and was near the top of her class in school until two years before, when she began to drop toward the lower third of the class. She originally was left handed, but "changed over" in school. At present, she is ambidextrous.

Examination.—The patient was well developed. She gave a good account of herself in relation to her environment and seemed keen and alert. General physical and neurologic examinations on admission gave normal results. All laboratory data were normal. An electrocephalogram showed greatest abnormality of waves on the right side, just ahead of the motor strip.

Operation.—On March 29, 1939, under anesthesia induced by avertin with amylene hydrate (70 mg. per kilogram of body weight), procaine (1 per cent) and ether, the body of the corpus callosum and the upper part of the genu were divided. Exposure was difficult, owing to dense adhesions between the two cingular gyri.

Postoperative Course.—Fourteen days after operation the patient had a series of attacks which were characterized, as a rule, by incontinence of urine and minor twitching of muscles of variable degrees. During some of these seizures she did not lose consciousness, but she did not talk. In others she lost consciousness for as long as ten minutes. One other attack occurred three weeks after operation, with loss of consciousness. The patient's mental condition was no different than before operation. After returning home she was able to do the usual housework, play the piano as usual, sing and sew.

On June 12 and 19 the patient had generalized seizures, which differed from previous ones in some respects. They were observed by younger children, who stated that she turned about several times—whether to the right or to the left is not known—and then fell to the floor. The patient remembered this part of the attack and recalled hearing her sister talk to her, but she could not answer. After falling, she lost consciousness. She bit her lip during the seizure. Sphincter control was lost in one attack. Otherwise, according to the mother, the patient is more normal than she has been for years. She is mentally keen and active, and works on the farm and about the house. Constipation, which had been obstinate for years, has been minimal since operation.

CASE 7.— *"Fainting spells," of twelve years' duration and attacks of petit mal and epileptic equivalents. Partial division of the corpus callosum.*

History.—C. N., a woman aged 36, was admitted to the hospital on March 23, 1939, because of fainting spells. The father was separated from the mother when the patient was 1 year of age. The mother soon remarried, and never mentioned the patient's father in the presence of the children. Nothing was known of the father or of his family history. The stepfather died at the age of 66, four years before the patient's admission. The maternal grandparents were of Norwegian stock. There was no history of nervous or mental disease in the family. The mother is living, at the age of 58; she is described as nervous and irritable. One brother is living, but his whereabouts are unknown. One sister is living and well. Three stepsiblings are living and well.

The patient was born on Jan. 11, 1902. She attended public schools in Alberta, Canada, and in Idaho and completed high school in Bethel, Vt. She received the degree of Bachelor of Science at Middlebury College, in Vermont, attended the School of Social Service at Cornell University and had a graduate course at Simmons' College, in Boston. She stated that she had taught home economics since graduation and had had several positions. Her occupational record was good.

Menses began at the age of 15. The patient was not prepared for it and she reacted poorly to the event. She had always had many girl friends, but not many men friends. She had reacted poorly to this situation. She was disappointed, for she had always hoped to marry and have a home of her own. The patient's habits were moderate. She was teaching school in the daytime, attending occasional movies and doing considerable reading after school. Her general health had always been good.

The tonsils were removed at the age of 16 because of hot, red, tender, swollen knees and ankles. A second tonsillectomy was performed in 1938 because of recurrent swelling of the joints. Appendectomy was done in 1926. In March 1938 she began to cough a great deal, and on five or six occasions coughed up 3 or 4 tablespoonfuls of bright red blood. The sputum was frequently streaked. Roentgen studies after the injection of iodized poppyseed oil revealed rather extensive bronchiectasis of the left lung.

Epileptic Seizures: In 1926, without preceding trauma or infection, the patient had the first seizure. It occurred at night while she was in bed, as did most of the succeeding attacks of this type. Practically all the attacks were associated with the menstrual period. She described a typical one as follows: Just before going to sleep, without an aura of any kind, "a wave beginning in the pit of the stomach would sweep up over my head as though a black curtain were drawn." Her thoughts and activity were momentarily suspended. There were no convulsive accompaniments, no autonomic phenomena and no loss of consciousness. She would then become alert and a little frightened. Five or six attacks such as this occurred each month. Another type of attack began about ten years ago. This was characterized by loss of consciousness, loss of bladder control, a tonic seizure and postseizural semistupor. She occasionally had these spells in the daytime, but still in association with the menses. The seizures lasted ten to fifteen minutes, and the patient might sleep afterward for as long as twenty-four hours.

In 1929 the patient had a grand mal seizure, followed by a period of furor in which she ran about the house, threw people about who were trying to restrain her, smashed furniture and was completely unmanageable. After this she had, in the semistuporous postseizural interval, repeated petit mal seizures without convulsive phenomena. She had had several episodes of furor after grand mal attacks.

On two occasions she had what amounted to status epilepticus, with from twelve to fifteen grand mal attacks, each lasting about fifteen to twenty minutes. At the time of admission she was receiving dilantin sodium, 100 mg. three times a day, and 1 grain (0.06 Gm.) of phenobarbital at night. This therapy had been somewhat beneficial. She had been on a ketogenic diet, also with some relief, but was receiving medication at the same time.

Examination.—The patient was tall, erect and composed. She was able to give a good history and showed clear insight into her difficulty. She had been a successful school teacher and had certain mannerisms of exactness associated with that profession. Neurologic examination on admission gave normal results. General physical examination revealed clinical evidence of bronchiectasis of the left lung, which was confirmed by roentgenograms. The pneumoencephalogram, taken at New Haven, Conn., was thought to show evidence of greatest abnormality in the upper part of the left motor area.

Operation.—On April 4, 1939, under anesthesia induced by avertin with amylene hydrate (70 mg. per kilogram of body weight) and 1 per cent solution of procaine the greater part of the genu and the body of the corpus callosum were divided. The splenium was left intact.

Postoperative Course.—Five days after operation the patient had a series of jacksonian attacks involving the right side, without loss of consciousness. The next day there was an attack involving largely the left side, with probable loss of consciousness. Since then she has had only one episode which in any way simulated the preoperative seizures. This occurred about six weeks after operation and consisted of a few hours of mental confusion, during which she was mildly agitated, called on God to witness her goodness and gave other such manifestations. A seizure did not follow. At present she is able to do housework; she reads long books and, to her family, appears no different than before operation.

Case 8.—*Convulsions; verified tumor (fibrillary astrocytoma) of the temporal lobe. Partial section of the corpus callosum.*

History.—E. C., a woman aged 43, was first seen on Jan. 4, 1937, because of convulsions for the preceding four years. The attacks started as fainting spells in the early morning. A hypoglycemic state as the cause was ruled out. An aura was lacking, as were lateralizing signs when the convulsions became the dominant feature. Incontinence occurred rarely, biting the tongue occasionally. Many petit mal seizures were experienced between attacks of grand mal, which occurred from three to twenty times a year. On March 16, 1937, a ventriculogram gave evidence of a tumor in the right temporal lobe. This proved to be a tough, hard fibrillary astrocytoma, and was removed in part. The anterior two thirds of the temporal lobe was excised down to the ventricle. Convalescence was uneventful, but the seizures continued as before, in spite of heavy medication. On readmission in April 1939 results of neurologic examination were still normal, and there was no evidence of increased intracranial pressure.

Operation.—On April 21, 1939, the upper portion of the genu and the body of the corpus callosum were divided under anesthesia induced by ether and avertin with amylene hydrate.

Postoperative Course.—Since operation the patient has had a number of dreamy states in which she may have slightly accelerated breathing and a blank look, and may momentarily stop reading or sewing. After her return home she was found on the bathroom floor on one occasion, but had not had a convulsion

so far as was known; she was conscious, but a little confused. Mentally, she is able to do everything she could before operation, including such activities as complicated cross word puzzles, knitting, sewing and reading. Her memory is as good as it has been in years. No changes in personality are noticeable to the examiner or to the family.

CASE 9.—*Convulsions since the age of 15, beginning two months after a fall in which the patient struck the back of the head; dazed but not unconscious during seizures. Complete division of the corpus callosum and left limb of the fornix.*

History.—A. M., a man aged 25, had been well up to the time of a fall, at the age of 15 years. Two months later the first of a series of convulsions occurred. The convulsions came without any warning. Unconsciousness was deep and sometimes protracted. At times sphincter control was lost, and the tongue bitten.

Examination.—The patient appeared husky, and general physical and neurologic examinations gave essentially normal results. He had lost all the fingers of the right hand as the result of an accident during a fit. He seemed to be above the average mentally for one of his limited education—he had reached the eighth grade—and to have good judgment and insight into his difficulty. Apparently he had not deteriorated mentally because of the attacks. All laboratory data, except the electroencephalographic findings, were within normal limits. There was an area in the right frontal region from which abnormal waves were fairly constant.

Operation.—On May 13, 1939, with anesthesia induced by avertin with amylene hydrate, local anesthetics and ether, complete section of the corpus callosum was made. The left limb of the fornix was also divided. A branch of the anterior cerebral artery to the right frontal lobe was injured in exposure and had to be clipped. The superior longitudinal sinus was ligated in the anterior end of the wound to gain better exposure. Two small right frontal cerebral veins were ligated for the same purpose.

Postoperative Course.—The patient had a stormy postoperative course. This may have been due in part to poor anesthesia—a considerable amount of obstruction having been present—and in part to the ligation of cerebral vessels or to possible thrombosis of cerebral vessels, about which nothing was known. Fever, of unexplained origin, continued for about four weeks. There was no evidence of infection of the wound or of meningitis. Because of the fever, fluids were given in amounts up to 3,500 cc. daily. This may have played a part in a series of postoperative convulsions. The convulsions began six days after operation and continued throughout the patient's stay in the hospital, in spite of the liberal use of phenobarbital. Most of the seizures were generalized and accompanied by incontinence of urine. A few jacksonian convulsions without loss of consciousness were noted.

CASE 10.—*Cerebrovascular accident at the age of 2; hemiplegia and athetosis on the left side and convulsions. Complete section of the corpus callosum and left fornix.*

History.—G. B., a boy aged 14, was normal at birth and until the age of 2 years, when he had laryngeal diphtheria. During this infection left hemiplegia occurred. The left side became spastic, and atrophy of moderate degree developed. Mentally, the patient was retarded and had continued so. He was regarded as a high grade defective person by the psychologic examiner. The first of a large series of convulsions occurred at the age of 8. Seizures varied in type and frequency. The majority occurred without an aura. Consciousness was lost early, and convulsive movements were bilateral. Sphincter control was at times lost. There

were other episodes of the nature of an epileptic equivalent, in which he might carry out curious ideas, whirl about like a dervish and sometimes fall. Petit mal seizures had also been noted.

Operation to lengthen a shortened achilles tendon was performed in 1934.

An encephalogram, made in 1935, gave evidence of moderate atrophy of the brain, more particularly of the right frontal region.

Examination.—The patient was a husky; his obvious defects were spasticity on the left side and mental deficiency. There were withering of the left arm and shortening of the left leg. He also exhibited athetosis of the left arm and, to a lesser extent, of the left leg.

Roentgenograms of the skull were noncontributory. Psychologic and psychiatric examinations gave a rating of high grade mental defectiveness. An electroencephalogram gave evidence of the greatest abnormality of brain waves from the left frontal area.

Operation.—On May 19, 1939, under anesthesia induced by procaine (1 per cent), ether and avertin with amylene hydrate, a bone flap in the right frontoparietal region was cut, the incision extending across the midline about 1 inch (2.5 cm.). A small defect in the longitudinal sinus was made, but bleeding was readily controlled by a muscle stamp. A large scar, 5 cm. in diameter, was encountered in the right premotor area. The corpus callosum was divided in its entirety, from the rostrum to the tip of the splenium. The left limb of the fornix was also divided. Only one small cortical vein needed ligation in exposure of the corpus callosum.

Postoperative Course.—The patient made an uneventful recovery from the operation. During the first forty-eight hours the athetosis of the arm and leg was definitely less than before. The spasticity also seemed to be less. However, before the patient's discharge from the hospital no change in the athetoid movements could be made out. The decrease in spasticity seemed to persist, and motion pictures of the patient appeared to show greater facility in movements of the shoulder and elbow.

The patient had a convulsion five days after the operation, the first convulsion he experienced during which there was sufficient time for him to observe the early manifestations. He stated that his head became hot, his eyes blinked, his jaw pulled to the left, and his left arm jerked; shortly thereafter he became dazed and possibly unconscious. During the seizure he carried out commands, but later did not recall doing so. On the sixth postoperative day he had about ten jacksonian seizures, but did not lose consciousness during any of them. He was able to talk to the nurses, to move about in bed and later to describe the events of the seizure. At this point the use of phenobarbital was reinstituted, and no further seizures have been observed to date.

OPERATIVE TECHNIC

The method used in this clinic for surgical division of the corpus callosum is as follows:

Avertin with amylene hydrate (70 mg. per kilogram of body weight), procaine in a 1 per cent solution and ether are used as a rule for anesthesia. Intravenous injection of saline solution during operation is also a standard procedure. It is found advantageous to place the patient on the operating table with the trunk and lower extremities on a dependent incline of about 35 degrees and to have some device for raising and lowering the head alternately. Any of the standard cutaneous incisions may be used for exposure of the right frontoparietotemporal region, and

of the left parasagittal region for 1 inch (2.54 cm.) lateral to the longitudinal sinus. Burr holes are made on each side of the longitudinal sinus just posterior to the coronal suture. An anterior burr hole to the left of the midline in the frontal area, about 2 cm. above the average frontal sinus, and another in the anterior temporal region (fig. 1) are made. The bone flap is cut with Gigli saws, except across the superior longitudinal sinus posteriorly, where a DeVilbiss rongeur is

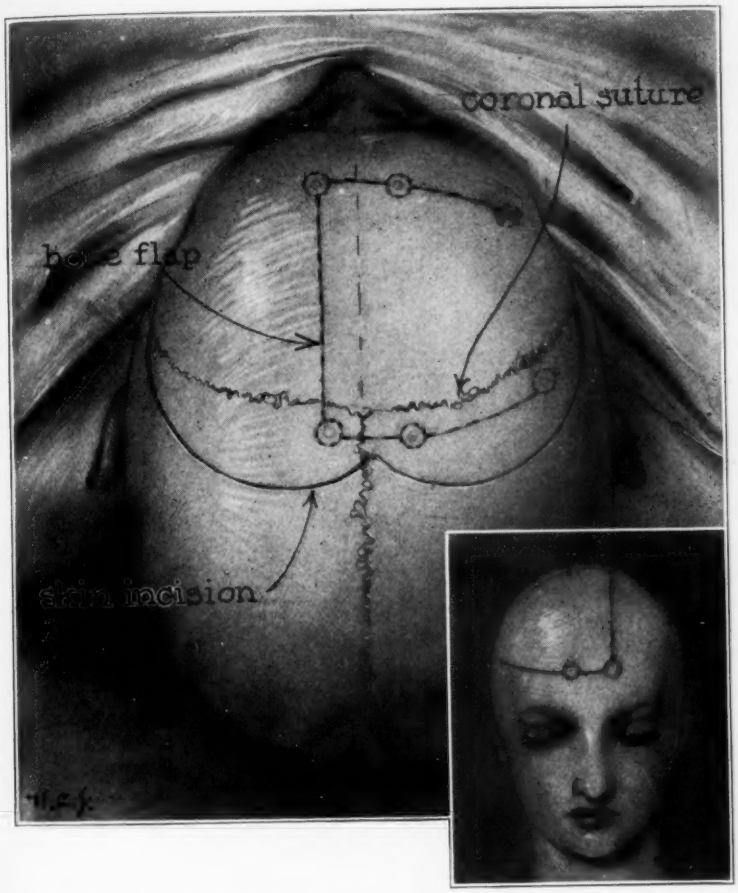

Fig. 1.—Drawing to illustrate the usual incision in the bone in relation to the coronal suture and the midline.

employed. The dura and the longitudinal sinus are depressed with cotton or bone wax. In only 1 instance was there troublesome bleeding from the longitudinal sinus. This was controlled with a muscle stamp. It is important to have the longitudinal sinus exposed for the whole length of the field. After ordinary bleeding points have been secured with the endotherm or clips, the dura is opened widely, with the pedicle along the longitudinal sinus. If adequate room for working is not obtained, the longitudinal sinus is ligated in the anterior

end of the wound along with the adjoining half or two thirds of the falx (fig. 2). There are usually two or three small veins entering the longitudinal sinus from the right frontal lobe, which must be divided.

The right frontal lobe is then retracted away from the falx until the anterior cerebral arteries are exposed above the anterior part of the body of the corpus callosum (fig. 3). Next, the fibers of this structure are divided with any suitable instrument and the lateral ventricle—usually the left—is opened. There is great variation in the arrangement of the anterior cerebral arteries. At times it is possible to work between the two, but more often it is necessary to work to the right or the left of both of them. After the body of the corpus callosum has

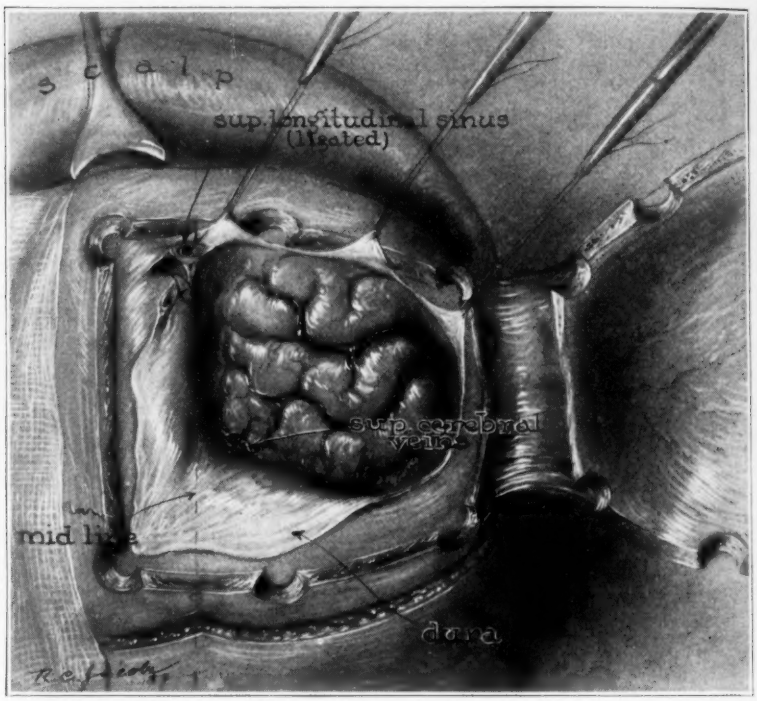

Fig. 2.—Drawing of the brain after exposure, showing the dura reflected across the longitudinal sinus, where it is left at closure. The dura is also brought out of the bone incision elsewhere. The longitudinal sinus has been ligated.

been completely divided the patient's head is elevated slightly and the genu cut until the anterior cerebral arteries can be visualized in the region of the rostrum. Then the head is lowered and the splenium divided. A curved suction tip is of considerable aid in this part of the procedure. During this stage of the operation the third ventricle is opened. The limb of the fornix may then be divided on one side just anterior to the foramen of Monro, or bilaterally where it joins the body of the corpus callosum. Painstaking hemostasis is naturally in order when the lateral ventricle has been so widely opened.

The dura is not closed, but rather is brought out of the edges of the wound at all points and sutured to the pericranium to prevent any possibility of an extradural accumulation of fluid. A piece of thin gutta-percha over the cortex during operation is useful, and may be left in place of the dura at the time of closure. The bone flap is tied in position with one silk ligature.

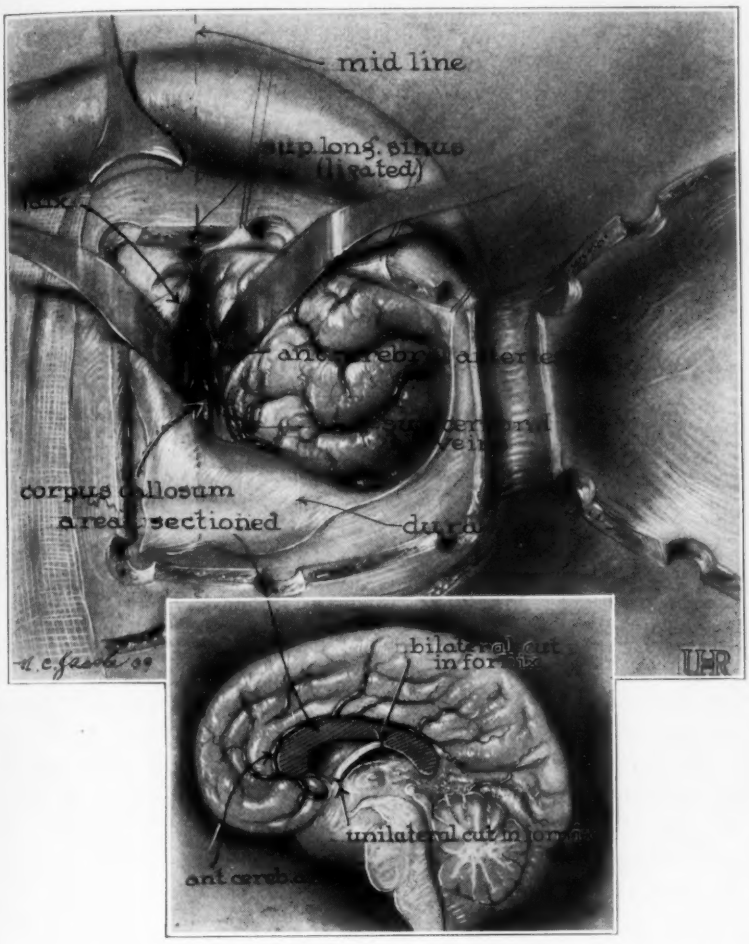

Fig. 3.—Exposure of the corpus callosum and sagittal section of the brain, showing the area of the corpus callosum cut, as well as the site of division of the fornix.

The patient is left on the operating table until fully conscious and then put in bed, with the head elevated to 15 degrees. There is usually an accumulation of cerebrospinal fluid and serum beneath the scalp, which may need aspiration at the end of twenty-four to forty-eight hours. In every case all medication—bromides, phenobarbital or dilantin—was withdrawn on the patient's admission, and

fluids were allowed in amounts up to 4,000 cc. a day in order that the effect on any seizures might be observed. When seizures have occurred and been observed, phenobarbital is reinstituted and fluids are limited to from 1,500 to 2,000 cc. a day.

COMMENT

It is appreciated that an adequate conclusion in regard to the effect of division of major commissural pathways on epileptic seizures cannot be reached on the basis of the cases of 10 patients who have been followed only a few months, from February 6 to July 1, 1939. However, it seems worth while to report certain observations made and to pursue this problem further. It is proposed to study the effect of section of various association pathways in a larger group of patients suffering from various forms of epilepsy, who can be followed for an indeterminate period.

Results of Operation.—The effect of surgical division of the commissural pathways as seen in the 10 cases studied may be outlined as follows: Associated movements of the two sides have hardly been affected. In none of the patients has there been any persistent dissociation of movements. One patient (case 3) made the following comment after the first stage operation: "The muscles of my left side do not coordinate very well with those of the rest of my body. For instance, I find myself trying to open a door with the right hand and at the same time trying to push it shut with the left; putting my dress on with the right and pulling it off with the left." This disorder was temporary and completely disappeared. Others were able to carry out all movements to which they were accustomed, such as playing the piano, sewing, knitting—with the eyes either open or shut—dealing cards, buttoning clothes and using common utensils. The patient in case 1 showed curious involuntary associated movements of the right, or atrophic, arm when the left hand or arm was moved either actively or passively. This phenomenon was observed on admission and was totally unchanged by section of the fibers of the corpus callosum. The patient in case 4 showed the same phenomenon, but to a lesser degree. The presence of bilateral representation of the arm area in one hemisphere was postulated to explain this association, particularly since the phenomenon persisted after operation.

Neither apraxia nor astereognosis was noted in any instance. Memory, the ability to calculate and to reason and other intellectual activities are the subject of a special study by Dr. A. J. E. Akelaitis and Dr. F. H. Parsons. In general, there did not seem to be any gross disturbance. One patient (case 3) complained of not being able to carry a tune after the first stage operation, admitting, however, that she was never adept at it.

Personality changes were not noted more frequently than in patients in general who undergo serious operations in the hope of relief from seizures. One patient, as already mentioned, referred to herself for a few days in the third person whenever questioned, saying, for example, "R. had a headache all morning."

Sphincter control was not disturbed except for a few hours after operation or during a generalized seizure, except in case 4. The child in this case had three petiti mal attacks associated with loss of bladder control after operation.

Hemiparesis, of a temporary nature, was noted in 2 patients (cases 2 and 9). The patient in case 2 is known to have had retrograde thrombosis of a fairly large cortical vein draining the right arm area. The patient in case 9 probably had a similar lesion. In both instances the weakness disappeard in two or three weeks, until none was perceptible on ordinary examination.

Studies of visual fields were made when the splenium was divided, without any alterations being detected.

Speech records of 3 patients were made for the sake of noting preoperative or postoperative changes in tone, pitch and other qualities. No appreciable variation from normal was noted.

Studies of the gait were made by Dr. R. P. Schwartz and Mr. Arthur Heath by means of the electric basograph; a separate report on this will be made. No gross variations from normal were apparent except those due to weakness and rest in bed.

Relief from constipation was an unexpected postoperative observation and is not thought to be due to changes in diet or habits. In the 2 patients on whom roentgen studies of the gastrointestinal tract were made, no gross changes in gastroenteric motility were noted.

Athetoid movements were little, if at all, changed by section of the corpus callosum (case 10).

Spasticity seemed to decrease, as noted in the arm movements in cases 1 and 4. The mother of the patient in case 4 is much impressed with his increased ability to use the spastic arm.

Electroencephalographic records, both preoperative and postoperative, will be the subject of a further report.

Postoperative Follow Up to July 1, 1939.—The patients had all been receiving phenobarbital, dilantin sodium or bromides at the time of their admission to the hospital. All medication was withheld during the preoperative and postoperative periods until a series of attacks could be observed. Fluid intake was gradually doubled in order to try to induce a seizure for purposes of observation.

In each case the postoperative seizures seen or reported up to the date of writing, July 1, 1939, are noted as follows:

Case 1.—After partial division of the corpus callosum, a few jacksonian twitchings occurred in the atrophic arm, without loss of consciousness. There were no generalized convulsions.

Case 2.—After partial division of the corpus callosum a series of generalized seizures occurred, beginning in the right frontal area (according to the description) and, as a rule, accompanied by loss of consciousness. After complete division of the corpus callosum and the body of the fornix, two seizures with loss of consciousness took place during administration of forced fluids and withholding of sedation; no seizures have occurred since the patient's return to the former regimen.

Case 3.—After partial division of the corpus callosum, a series of attacks occurred without loss of consciousness; later attacks were characterized by loss of consciousness and of sphincter control. Since complete division of the corpus callosum, there have not been any generalized seizures.

Case 4.—After partial division of the corpus callosum there have been no generalized seizures; three "blank spells," probably petit mal attacks, occurred. There is occasional bed wetting, but no seizures.

Case 5.—After partial and complete division of the corpus callosum, there were generalized seizures with and without loss of consciousness, which were closely related to the menses.

Case 6.—After partial division of the corpus callosum, there have been definite loss of consciousness, biting of the tongue and loss of sphincter control.

Case 7.—After partial division of the corpus callosum, there have been no further convulsive seizures; one or two periods of mental confusion have occurred. A jacksonian fit on the right side, without loss of consciousness, was observed while the patient was still in the hospital; the next day a similar phenomenon occurred, except that it involved the left side. (It seemed certain that the epileptic wave did not spread to more than one hemisphere.)

Case 8.—After partial division of the corpus callosum, it is probable that seizures with loss of consciousness have not occurred. There were several petit mal seizures: The patient was known to have fallen once, but no convulsion was reported.

Case 9.—After complete division of the corpus callosum and the left limb of the fornix, many generalized seizures occurred during the immediate postoperative course, and were accompanied by loss of consciousness and incontinence. The patient was thought to have had postoperative thrombosis of cortical veins, leading to temporary hemiparesis.

Case 10.—After complete division of the corpus callosum and the left limb of the fornix, a series of jacksonian attacks without loss of consciousness occurred.

The impression is gained from this small number of observations that the type of case in which section of commissural fibers in the corpus callosum is most favorable is the one in which a large cortical or subcortical scar exists, as in cases 1 and 10. Whether section of various commissural pathways to prevent the spread of an epileptic wave is indicated for patients having multiple irritable foci is a matter for future study. Theoretically, there is no reason why attacks should

not start in the two hemispheres simultaneously and be unaffected by section of any pathway. The impression is gained that this must occur in certain types of conditions, such as in those associated with insulin and metrazol therapy, as well as in hypoglycemic states. The observation on patients having jacksonian seizures on the right side after section of the corpus callosum on one occasion and on the left side on another suggests that there are at least bilateral foci from which seizures may originate (case 7).

The inhibitory effect of the cortex of one hemisphere on the activity of the other must also be considered seriously. There seems no reason to doubt that in certain states, such as stammering, the cortex of the dominant hemisphere eventually exercises inhibitory influences on the opposite hemisphere. It may be that in certain instances the cortex of one hemisphere may inhibit abnormal activity of an abnormal zone and that section of commissural pathways is contraindicated.

In addition to the effect of section of commissural pathways from one hemisphere to the other, that of section of association pathways within the one hemisphere is a matter for further consideration.

CONCLUSION.

Section of the commissural pathways contained in the corpus callosum may be carried out without any untoward effect on the patient. Such a section may serve to limit the spread of an epileptic wave to the opposite hemisphere. When such limitation occurs, the patients do not seem to lose consciousness or have generalized convulsions. When there are multiple areas from which an epileptic seizure may originate, possibly simultaneously, section of commissural pathways between hemispheres may not have any influence on the seizures.

FARADIC SHOCK IN TREATMENT OF FUNCTIONAL MENTAL DISORDERS

TREATMENT BY EXCITATION FOLLOWED BY INTRAVENOUS USE OF BARBITURATES

NATHANIEL J. BERKWITZ, M.D., PH.D.
MINNEAPOLIS

The courageous pioneer work of Sakel and Meduna has opened wide horizons in the field of psychiatry. When shock treatment was first introduced it was believed to be specific for schizophrenia, but now it is generally considered as a valuable adjuvant to psychotherapy in the treatment of many types of functional mental disorders. The majority of workers have found that the incidence of improvement or recovery with insulin hypoglycemic and metrazol convulsive shock therapy is greater than the rate of spontaneous remission. Although encouraging success has been obtained with this treatment, serious complications, such as fractures, lesions of the brain and abscesses of the lung, and even an occasional fatality have retarded the general adoption of such therapy.

In order to avoid some of the dangers met in metrazol therapy, Cerletti and Bini,[1] in 1938 applied electric currents of as high as 300 to 600 milliamperes and 80 to 115 volts to the patient's head for a fraction of a second to produce convulsions and unconsciousness. In 1939, Sogliani;[2] Kalinowsky;[3] Fleming, Golla and Walter,[4] and Shepley and McGregor[5] claimed gratifying results with this technic. Whether electric or metrazol convulsive therapy is safer remains to be proved. Kalinowsky drew attention to a conceivable danger, cerebral damage, only to dismiss it.[6] Two cases of fractures of vertebrae with this seemingly drastic method have already been reported.[7]

1. Cerletti, U., and Bini, L.: L'elettroshock, Policlinico (sez. prat.) **45**:1261 (July 4) 1938.

2. Sogliani, G.: Eine neue Methode der Krampftherapie, Deutsche Ztschr. f. Nervenh. **149**:159-168, 1939.

3. Kalinowsky, L.: Electric-Convulsion Therapy in Schizophrenia, Lancet **2**:1232-1233 (Dec. 9) 1939.

4. Fleming, G. W. T. H.; Golla, F. L., and Walter, W. G.: Electric-Convulsion Therapy of Schizophrenia, Lancet **2**:1353-1355 (Dec. 30) 1939.

5. Shepley, W. H., and McGregor, J. S.: Electrically Induced Convulsions in the Treatment of Mental Disorders, Brit. M. J. **2**:1269 (Dec. 30) 1939.

6. More Shocks, editorial, Lancet **2**:1373 (Dec. 30) 1939.

7. Blair, D., in Discussion on Electrically Induced Convulsions, Brit. M. J. **1**:104-106 (Jan. 20) 1940.

The use of electricity in the treatment of mental disorders is not recent. In a previous paper, I [8] cited several workers in the nineteenth century who used electricity in the treatment of mental disorders. Some of their results compare favorably with those of shock therapy today.

In an outstanding comprehensive survey of psychotherapeutics published in 1925, Janet [9] championed "treatment by excitation." He expressed the belief that there is a lowering of psychologic tension in psychoses and that treatment by excitation raises the subject's tension to the level at which effort becomes possible. He predicted: "Some day perhaps electricity will be one of the most valuable among the agents that can modify and stimulate these patients." In a preliminary report,

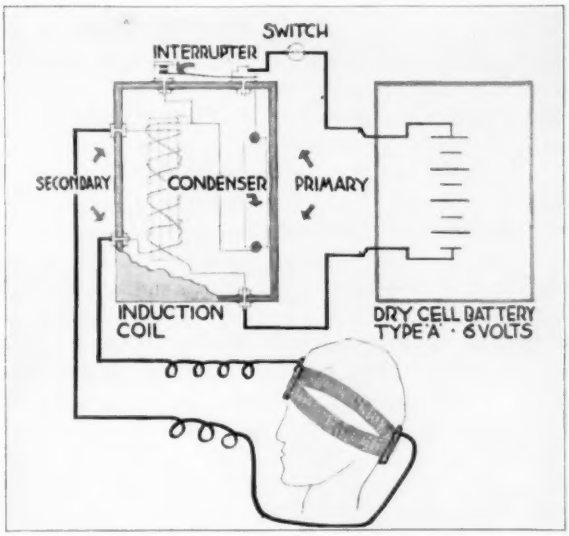

Diagram of the induction coil and manner in which the electrodes are placed for treatment with faradic shock.

I [8] recently introduced a psychophysiologic method of excitation, using a faradic current well within the margin of safety. Immediately after the electrical stimulation a barbiturate is administered intravenously.

APPARATUS AND TECHNIC

A few minor changes in technic have been made since the first report was published. A faradic current is produced by an induction coil (model T Ford spark coil), which is energized by a 6 volt dry cell battery, type A. Although

8. Berkwitz, N. J.: Faradic Shock Treatment of the "Functional" Psychoses, Journal-Lancet **59**:351-355 (Aug.) 1939.

9. Janet, P.: Psychological Healing, translated by E. Paul and C. Paul. New York, The Macmillan Company, 1925, vol. 2.

the no load or open circuit secondary voltage produced by the induction coil is about 20,000, the terminal voltage drops tremendously, even under a small current drain. Since the classic relationship expressed by Ohm's law does not hold with organic tissues, the following procedure was employed to determine the order of magnitude of the average current which passes through the head of the patient. First, the resistance between two electrodes placed on the forehead and neck was measured on several persons with a direct current ohmmeter. This resistance varied by a few thousand ohms, but the average was found to be approximately 10,000 ohms. A resistance of 10,000 ohms was then connected with the output terminals of the induction coil. The output voltage with this resistance, as measured with a rectifying voltmeter, was found to be approximately 100. The average current was found to be about 10 milliamperes. A much higher current than this is often used clinically in muscle and nerve stimulation and in diathermy treatment (high frequency current) without producing tissue damage. The potential used in electric convulsive therapy is about fifty times as strong. Therefore, no tissue damage from the effects of heating is to be anticipated with the faradic current described in this paper, and the current can be safely tolerated by patients with no vascular disease. With electrodes placed on the head, little if any current is conducted to the heart.

It has been found advisable to hospitalize the patient for several days before the treatment is instituted, to allow him to become adjusted to his new environment. It is also recommended that the treatment be given when the stomach is empty, to avoid possible nausea from the intravenous medication.

A uniform introductory talk is given to each patient. He is informed before the first treatment, or as soon as adequate contact can be established, that he is a victim of a vicious cycle. He is told that his fears have created phobias, hallucinations and delusions (or whatever symptoms he may have) and that they in turn create new symptoms. He is further assured that he will recover, but that by means of this treatment the vicious cycle can be abolished more quickly. Reassurance, as well as suggestion, is introduced by such an explanation.

Two Cambridge electrocardiograph electrodes fastened to a strip of rubber (electrode bands) are applied to the patient's head so that one electrode is placed on the forehead and the other on the neck. Cambridge electrode jelly is used to obtain good contact. Fifteen tetany-like shocks, each of approximately one-half second's duration, are given at intervals of one-half second.

Immediately after a series of electrical shocks are given, a barbiturate is injected intravenously. Pentothal sodium (sodium ethyl [1-methylbutyl] thiobarbiturate) and sodium amytal (sodium isoamylethylbarbiturate) have been used, pentothal sodium being given in most cases. This drug has been employed successfully since 1935 as a general anesthetic for short operative procedures. From 3 to 8 cc. of a 5 per cent solution (50 mg. per cubic centimeter) is injected slowly, as recommended by its manufacturers. With this drug, surgical anesthesia is produced in from thirty seconds to one minute. Unconsciousness lasts several minutes or more, depending on the amount of drug administered. The physician should be present when the patient awakens, to give him psychologic treatment. For noncommunicative and stuporous patients, when rapport or conversation is desired, 3 to 6 cc. of a 10 per cent solution (100 mg. per cubic centimeter) of sodium amytal is used intravenously. With the administration of a subanesthetic dose a short phase of excitement occurs. All barbiturates produce a short phase of excitement, but with pentothal sodium this effect is minimal, as the patient almost immediately goes into deep sleep. When sodium amytal is used, the injection is

stopped when the facial muscles twitch or changes of expression occur. The patient is then urged to talk and is not permitted to fall asleep. He usually talks more freely, shows more expression and often gives information not obtained previously.

Intravenous injection of pentothal sodium produces sleep more quickly, and the drug has a higher therapeutic index than the other barbiturates. Intravenous use of barbiturates is safe if one is well versed in the administration and dangers. Respiration must be watched carefully, for if an overdose is given respiratory failure may result. If the respirations should become irregular, stimulation with a few faradic shocks or artificial resuscitation quickly revives the patient. If an emergency should arise and respiration cease, intravenous administration of metrazol or some other strong respiratory stimulant is recommended, but in over one thousand injections of pentothal sodium no such emergency has arisen. When only small veins are encountered a more dilute solution (2.5 per cent) is used to prevent sclerosing.

From ten to twenty daily treatments were given in the majority of cases. This method is relatively simple and inexpensive, and each treatment takes approximately one minute to administer. It is understood, of course, that for the best results, as in all forms of shock treatment, considerable time must be spent in carrying out psychotherapy. One of the most important reasons for the difference in the results reported by various workers may well be the difference in appreciation and application of this requirement.

REPORT OF ILLUSTRATIVE CASES

CASE 1.—Mrs. E. S., aged 34, a housewife, had been quiet and introvertive for many years. In August 1938 she moved into an apartment building, which she disliked, as she had never lived in one before. In April 1939 she experienced ideas of reference, thinking the neighbors were talking about her because she praised her husband to them. A month later there appeared auditory hallucinations, and gradually she became more disturbed. Voices told her that she was "no good" and that she should end her own life. When admitted to the Minneapolis General Hospital on May 11, 1939, she refused to talk, stood motionless for long periods and appeared dejected and depressed. One night she became much disturbed because she believed she heard over the radio that her husband and two children were killed. She showed odd and negativistic conduct and frequently misidentified people.

Seven daily faradic shock treatments, with intravenous injection of 6 cc. of a 5 per cent solution of pentothal sodium, were given. The hallucinations ceased after the fourth treatment, and she began to talk more freely and rationally. After the sixth treatment she became more sociable and showed better insight. She was discharged on June 5, 1939 as markedly improved and spent the rest of the summer at a lake cottage. At several interviews, during a period of two months, no evidence of mental aberrations could be elicited. She expressed appreciation for what had been done for her and appeared to get along well. (This case was discussed as case 1 in my previous paper.) In the middle of August 1939, when her husband rented another apartment, she gradually became depressed again, and auditory hallucinations returned. She attempted suicide by slashing her wrist and was readmitted to the hospital on Aug. 28, 1939. She was given six more faradic shock treatments. She responded more promptly than before and left the hospital on Sept. 11, 1939, in a markedly improved condition. On April 13, 1940, when last interviewed, she had no further mental aberrations and appeared to be making

a satisfactory adjustment. She was doing her own housework and increasing her social contacts. No good understanding of the genesis of her psychosis could be formulated in this case.

In this case the psychosis was characterized by shifting and unsystematized paranoid trends, accompanied by hallucinations, depression of mood and total lack of interest. After responding to faradic shock treatment, the patient had a relapse, but promptly improved with further treatment. It appeared that both attacks were precipitated when her family moved into an apartment building (she expressed an intense dislike for apartments). The classification of the condition may be debatable; some might call it an acute paranoid psychosis, but many will agree with the diagnosis of paranoid schizophrenia. The result of treatment was remission.

CASE 6.—E. R., aged 22, a truck driver, had, according to his father, always been shy and sensitive, but was an average student in school. In the latter part of April 1939 he became talkative and excitable. His condition continued to grow worse, and he was admitted to Homewood Hospital on May 29, 1939, as a patient of Dr. Julius Johnson. He warned the nurses not to touch him, as G men were his friends, and he talked a great deal about religion. He tried to jump out of a window, laughed for no apparent reason and frequently jabbered disconnected thoughts. On June 4, 1939 there developed an attack of acute appendicitis, and operation was performed on the following day. Peritonitis developed, and a septic temperature continued until June 25, 1939. During this period his behavior changed. He became more confused and disoriented, although he had occasional lucid intervals. As he recovered from the somatic complication the psychotic symptoms present before the attack of appendicitis reappeared.

Beginning on Aug. 3, 1939, nine faradic shock treatments were given, with injections of 8 cc. of a 5 per cent solution of pentothal sodium. The patient began to improve after the second treatment, and after the sixth treatment talked more rationally but was still overtalkative. He continued to show improvement, becoming more rational and willing to read. On Aug. 27, 1939 he was discharged as markedly improved. A letter from his parents three months later stated that he had returned to his previous occupation and that he had "entirely recovered."

The outstanding clinical features were acute excitement, scattered and bizarre delusions and hallucinations. Physical examination on admission to the hospital gave essentially normal results, and no evidence of a toxic condition was found at that time. The clinical picture changed when a septic condition appeared, but the original symptoms returned when the infection subsided. The psychosis in this case can properly be called acute schizophrenia, with temporary toxic delirium in the interim. The result of treatment was remission.

CASE 9.—Miss R. B., aged 37, a practical nurse, had been in good health until the age of 16. She then missed school often because of severe menorrhagia. She gradually withdrew from her friends and became more seclusive. At the age of 22 she was graduated from high school as salutatorian. She obtained a position as cashier, but gave it up because she "worried too much" when her books did

not balance. On a few occasions she had attacks of numbness in her left arm (apparently hysterical). She did not work for several years because she felt incompetent and unable to concentrate. At 30 years of age she became a practical nurse, but felt that patients did more for her than she did for them. She never went with men because she said that she was afraid she might fall in love and that she could not be a worthy wife. Her condition continued to grow worse, until she was admitted to the Minneapolis General Hospital on June 23, 1939. She was depressed, heard voices and refused to mix with other patients. She gave a story of being kidnapped, placed in a sack and carried away by two strange men. She told of hearing remarks that she was "out of the gutter and a streetwalker."

Beginning on June 26, 1939, eleven faradic shock treatments were given, with injections of 5 cc. of a 5 per cent solution of pentothal sodium. After the third treatment she said she no longer heard voices. After the seventh treatment she became more alert, expressed great faith in the treatment and started conversations with other patients. On July 10, 1939, she volunteered the statement: "I feel as if I had shed something, an outer shell of some kind," and expressed gratitude for what had been done for her. She stated that the stories of being kidnapped and the ideas of people talking about her must have been products of her own imagination. She was discharged on July 22, 1939 as markedly improved, and moved to the country to live with relatives.

In answering a letter from me in October 1939, she stated that she was doing housework and was getting along well. During February 1940 she again gradually became apathetic and seclusive; she returned to the hospital on March 28. After three faradic shock treatments she showed decided improvement, with more interest and animation. She denied having had any hallucinations since she was treated with faradic shock treatments during her first admission to the hospital. She said: "My mind felt as if it were asleep the last month." Although she was somewhat retiring, she was cheerful, showed good insight at the time of her discharge (on April 15, 1940) and expressed willingness to secure employment.

In this case there was evidence of a long-standing series of maladjustments, terminating in a psychosis. The patient was depressed and had paranoid ideas, accompanied by visual and auditory hallucinations. Some might call the condition a paranoid state, but I classified it as paranoid schizophrenia. In any case such a long history with so prompt a response appeared remarkable. Although she had a relapse six months after treatment, she responded promptly after she was given three more faradic shock treatments. At the time of her second discharge it was believed that if she could secure employment and be given moral guidance she might make a good adjustment. The result of treatment was marked improvement.

Case 12.—Mrs. J. S., aged 31, a housewife, at 20 years of age had married a divorcé twenty years older than herself; he had three children only a few years younger than she. She became the mother of two children. She gave a history of having obsessive thoughts during the four years before admission, such as being afraid of rats and of being alone. A year previous to her present illness she refused to remain in a lake cottage which her husband had leased, even after an exterminator assured her that the house was free of rats. A few days after her

brother died, on July 11, 1939, she became hysterical. She became talkative and restless, and a week later was admitted to Homewood Hospital in a markedly disturbed condition. At first she behaved like a person with acute mania. She tore off her clothes, and her speech was flighty and disconnected. She refused to eat because she believed that her husband ordered her food to be poisoned. She later showed definite schizoid behavior, such as staring at the ceiling with a foolish grin, and gave evidence of having changeable and transitory hallucinations and delusions. Her behavior became queer and incomprehensible.

Beginning on July 28, 1939, eight faradic shock treatments were given, with injections of 6 cc. of a 5 per cent solution of pentothal sodium. Before the second treatment she said: "Kill me, I don't want to live"; but before the third treatment she appealed: "Kill me, do anything, but don't give me any more treatments." After the third treatment she began to improve. She became quiet and cooperative, and took the next five treatments willingly. She then confessed that her husband's son was the father of her youngest child, 4 years of age. Although the husband apparently was not aware of this fact, it worried her a great deal. Apparently improved, she was taken home on Aug. 9, 1939, but then felt that she should get a divorce. She quarreled with her husband, told him of her indiscretions and again became markedly disturbed. She was readmitted to the hospital on Aug. 29, 1939. She complained that other women patients were making sexual advances toward her, and was often observed to be masturbating. She was noisy and disturbed, argued with imaginary persons and exhibited causeless laughter.

She was again given eight faradic shock treatments. Improvement was noted after the second treatment. A more complete story of her past was then obtained. She told of the delusions and hallucinations she had had in her first two acute attacks, and of how she believed a gardener who was pruning bushes in their yard was employed by her husband to hide morphine in the bushes. On Oct. 18, 1939, she had an impacted tooth removed. Although she dreaded the extraction, fearing she might again have a relapse, the operation did not set her back as she anticipated. She regained more insight and talked more about her past life with normal emotion. She no longer felt bitter toward her husband and wrote him pleasant letters. On Dec. 2, 1939, she left the hospital and went on a trip with him. Within a few days she again quarreled with him and became depressed. She attempted suicide by hanging and was returned to the hospital for further treatment on Dec. 17, 1939. Her mental behavior was much different than it had been in her two previous hospitalizations. She constantly wrung her hands, and her mood was more that of anxiety and uneasiness. No hallucinations could be elicited at this time.

After three faradic shock treatments she became more cooperative and talked more freely. She was discharged on Jan. 10, 1940, as recovered. Her family moved to another city; four months later, according to the husband, she had completely recovered.

This patient tried to hide from an unfortunate experience for four years. During this period she showed obsessional tendencies. Immediately after her brother's death there developed an acute psychosis. She first had symptoms of hysteria, then manic excitement and later schizoid manifestations. Delusions of persecution and visual and auditory hallucinations developed, and she exhibited queer behavior, silly grimaces and sudden outbursts of excitement. In this case there were

many features of both acute mania and paranoid schizophrenia. Apparently, she was released from the hospital too early, but responded quickly to further faradic shock treatment. After quarreling with her husband again she had a second relapse. Her symptoms at this time were more like those in anxiety depression. She responded rapidly after receiving three faradic shock treatments and has remained well since. This case was diagnosed as one of paranoid schizophrenia. The result of treatment was remission.

CASE 16.—H. R., a man aged 23, unemployed, was a good student up to 15 years of age but began to fail in his studies in the second year of high school. He claimed that it was "from too much smoking." He refused to return to school that year and had not worked since. His parents separated when he was 9 years of age. Since, he had lived with his father and a younger brother. He would not go out and refused to do any kind of work. In December 1938 he no longer read and found it difficult to concentrate. In the following June he began to have auditory hallucinations. He complained of headaches and difficulty in urination. He expressed the belief that his brain was gradually being replaced by blood, which was "gushing" to his head.

On Oct. 12, 1939, he was admitted to the Minneapolis General Hospital. He imagined that syphilis was being spread to members of his family and to other innocent victims. He said that voices talked to him by mental telepathy, and that his mind was controlled by outside forces. He preferred to be left alone and showed lack of affective response.

Seventeen faradic shock treatments were given, with from 7 to 9 cc. of a 5 per cent solution of pentothal sodium solution intravenously. After the third treatment he said that he no longer heard voices. After the fifth treatment he began to show interest in his surroundings. On questioning, he admitted worrying about masturbation. He read and conversed with other patients, and smiled often. He was discharged on Nov. 15, 1939, at which time he expressed a desire to obtain work and to be more sociable. He still continued to show shallowness of affective response and shyness when he left the hospital. Four months later his father said that the patient "took more interest in things and that he was still trying to find work."

Clinical symptoms began to appear eight years before, but acute symptoms had been present for at least five months. The change in behavior, of eight years' duration, with symptoms of delusions of persecution, auditory hallucinations and general habit deterioration, presents in this case a diagnosis of paranoid schizophrenia. The result of treatment was marked improvement, with a questionable prognosis for the future.

CASE 33.—Miss O. A., aged 47, a school teacher, gave a history of having had three previous attacks of depression; however, she had not been hospitalized on any of these occasions. The first depression occurred seven years before. Each depression lasted about three to four months. In May 1939 she became overactive. She said that she seemed to accomplish more in her work, and that she entered into more social activities than she ever had in the past. In July she became

depressed, refused to leave her home, appeared despondent and apprehensive and cried easily. She was admitted to Glenwood Hills Hospital, as a patient of Dr. A. Dumas, on Aug. 17, 1939.

She received seven faradic shock treatments with injections of 5 cc. of a 5 per cent solution of pentothal sodium, and showed improvement with each successive treatment. She told the nurses and patients how much the treatments benefited her, and because of her improvement she encouraged and cheered other patients. On Aug. 28, 1939 she was discharged; she returned to school the following week. She has attended to her routine duties regularly and has been making a good adjustment for seven months.

This patient had had a recurrent illness for seven years. Although the last attack did not appear severe, the prompt response to treatment was striking, and there can be little doubt that the course was shortened by the faradic shock treatment. The diagnosis was manic-depressive psychosis, depressed type. The result of treatment was remission.

Case 34.—Mrs. L. R., aged 54, a housewife, twenty years before had had an attack of depression, which lasted four months. Her sister had had a similar attack a few months before. The patient did not make friends easily and was always sensitive and retiring. Her husband was a traveling salesman, and she was left alone for two or three weeks at a time. In August 1938 they moved into a new home. Shortly after they moved she complained of being afraid of living alone and worried needlessly about financial matters. She was taken to a rest home in October. She failed to improve after two months of hospital care, and was taken home. She continued to complain of not having proper clothes to wear and refused to dress. She constantly wrung her hands and expressed considerable anxiety. She was taken to a state hospital as a voluntary patient in April 1939, but the husband took her home after a few weeks because she disliked it. She continued to grow worse and was admitted to Glenwood Hills Hospital on Aug. 13, 1939.

She received ten faradic shock treatments, with injections of 5 cc. of a 5 per cent solution of pentothal sodium, and showed improvement after the third treatment. After the tenth treatment she appeared to be greatly improved. The husband was then permitted to see her, but she told him that the treatments were not helping her. He ordered the treatment discontinued and placed her in the care of another physician. She immediately grew worse after this, and two months later she was taken home, unimproved. According to the husband, she showed marked improvement as soon as she returned home.

This was the second attack of manic-depressive psychosis, depressed type. Although the patient seemed to improve with treatment, she influenced her husband to have it discontinued. She then showed signs of remorsefulness about this and immediately became more depressed. The result was temporary response to treatment, and, two months later, a spontaneous remission immediately after leaving the hospital.

Case 39.—H. D., a man aged 29, a laborer, married, with two children, the youngest of whom was 4 weeks of age, had been out of work for some time, although he tried hard to find employment. He worried and brooded because of failure to obtain work. He left home to seek employment on the morning of Aug. 29, 1939, and was picked up by the police the same evening. He was taken to

the Minneapolis General Hospital for observation, because he could not recall his name or where he lived. In the hospital he failed to recognize his wife and mother on four occasions. He appeared composed and tried to cooperate, but was unable to recall his identity. An intravenous injection of sodium amytal was given with the hope of obtaining information by narcoanalysis, but this proved unsuccessful. Four days later faradic shock treatment was started. After the second electric shock he cried out: "B-B-B-Beatrice." When asked who Beatrice was, he immediately replied: "My wife." He then pleaded that the treatment be stopped, for he could recall everything. No further shocks were given, and he was discharged the same evening, apparently recovered.

This patient brooded for several weeks because of inability to procure employment. After a period of emotional conflict, hysterical amnesia developed. The result was remission before completion of the first treatment.

SUMMARY OF RESULTS

The term faradic shock treatment has been chosen for the method described in this paper. The word "shock" is used to denote sudden and intense stimulation. A faradic (interrupted) current is employed to produce a maximal amount of stimulation with a minimal amount of current. The current used is well within the margins of safety. It does not cause burns and is not powerful enough to produce dangerous effects, such as unconsciousness, or irreversible physiologic changes. The patient is not even momentarily stunned, although momentary excitement and fear are produced. When stimulated the patient invariably shuts his eyes tight and holds his extremities rigid. The muscles of the face and neck contract spasmodically with each shock. The face is flushed, the pupils are dilated, the pulse rate is increased, the blood pressure is elevated and salivation is increased. All of these manifestations are evidences of physiologic stimulation. As with insulin and metrazol shock treatment, the blood pressure is elevated about 20 to 40 mm. of mercury immediately after the faradic shocks are given, but an hour after the treatment the blood pressure generally drops to about 5 to 15 mm. of mercury below the initial reading.

Pentothal sodium or sodium amytal, the amount varying according to the patient's need, is administered intravenously immediately after the faradic shocks are given. Pentothal sodium is generally used unless the patient is stuporous and uncommunicative. These drugs are given for the following reasons: (1) to relieve the patient of emotional excitement and apprehension frequently induced by the electric shocks, (2) to determine the mental content of noncommunicative patients, (3) to increase the patient's susceptibility to psychotherapy and (4) to produce relaxation or sleep after exciting the patient. On several occasions when the intravenous injection of a barbiturate was omitted intentionally, the patient remained restless and apprehensive after the faradic shocks.

The results obtained from the treatment have been classified as remission, marked improvement, slight improvement and no change. A patient was regarded as having a remission if he was free of the complaint which incapacitated him, if he showed good insight and realized that his ideas and behavior had been abnormal and if he was ready to resume, or had already resumed, his normal activity in the community. He was classified as showing marked improvement if he made a social recovery and returned, or was ready to return, to his previous or an equivalent occupation, though he still retained minor signs and symptoms, such as irritability, shyness and shallowness of affective response. Patients with slight improvement showed benefit from the treatment by becoming more manageable at home or at the hospital, but were not capable of pursuing any gainful occupation.

No patient was given more than twenty-two treatments. Although the course of treatment is completed in less than three weeks, most of the patients are kept in the hospital at least two weeks more for further psychotherapy and observation. In the majority of cases improvement was observed after the third or fourth treatment. Similar observations have been made by others, using metrazol convulsive [10] and electric convulsive [4] shock therapy. With few exceptions, from this point the patients either continued to show improvement with further treatment or had a relapse. Even the patients whose condition was considered to be unchanged had temporary improvement between the second and the fifth treatment. It appears that the patient loses some of his symptoms, regains some insight and tries to decide whether or not he wants to face reality at that time. It has been observed that in the successfully treated patients there are lessened tension and increasing amiability and friendliness with the physician with each successive treatment. Many objected to the treatment because of its unpleasant nature, but others submitted to it because they felt that they were being relieved of their unpleasant psychotic symptoms. Patients showing no sustained improvement usually continue to offer resistance. Some of the patients who were considered improved had a relapse after they were discharged, but some (cases 21 and 34) who failed to maintain improvement in the hospital and were discharged as showing "no change" improved immediately after leaving the hospital.

In a period of ten months, 73 patients with various mental disorders were given faradic shock therapy. I treated 27 such patients at the Minneapolis General Hospital and 18 at private hospitals (tables 1, 2 and 3). In addition, 28 were treated at two Minnesota state hos-

10. Dynes, J. B.: Undesirable Mental Sequelae to Convulsant Drug Therapy, J. Ment. Sc. **85**:494-497 (May) 1939. Schilder, P.: Notes on the Psychology of Metrazol Treatment of Schizophrenia, J. Nerv. & Ment. Dis. **89**:133-144 (Feb.) 1939.

TABLE 1.—*Results in Treatment of Schizophrenic Reaction Types with Faradic Shock*

Case Number and Name	Sex and Age	Marital State	First Prepsychotic or Psychotic Symptoms	Duration of Present Psychosis	Type of Schizophrenia	Number of Treatments	Results
1* E. S.	F 34	Married	2 mo.	6 wk. 2 wk.	Paranoid	7 7	Remission; relapse 2 months later; remission (see case report)
2* S. N.	M 20	Single	4 yr.	4 mo.	Hebephrenic	4	No change
3† R. K.	F 42	Single	10 yr.	4 mo.	Catatonic	14	Slight improvement
4* M. H.	M 38	Single	16 yr.	3 yr. 2 mo.	Catatonic	20 2	Marked improvement; relapse 7 months later; marked improvement
5† C. F.	M 28	Single	8 yr.	3½ mo.	Catatonic	12	Marked improvement
6† K. R.	M 22	Single	3 yr.	1 mo.	Mixed	9	Remission (see case report)
7† G. B.	F 46	Divorced	5 yr.	11 mo. 1 mo.	Mixed	15 3	Marked improvement; relapse 4½ mo. later; marked improvement
8† L. R.	F 25	Married	8 yr.	2 mo.	Paranoid and catatonic	13	Slight improvement
9* R. B.	F 37	Single	7 yr.	2 mo. 2 mo.	Paranoid	11 3	Marked improvement; relapse 9½ mo. later; marked improvement (see case report)
10* O. H.	M 38	Single	20 yr.	6 mo.	Catatonic	16	No change
11* M. W.	F 48	Single	14 yr.	1 wk.	Paranoid	11	Remission
12† J. S.	F 31	Married	4 yr.	17 days 2 wk. 11 days	Paranoid	8 8 3	Marked improvement; relapse 3 weeks later; marked improvement; relapse 3 weeks later; remission (see case report)
13* L. E.	M 29	Married	14 yr.	3 mo.	Mixed	22	Slight improvement
14* M. M.	F 54	Married (twice)	3 yr.(?)	3 yr.	Hebephrenic	9	Slight improvement
15* G. A.	M 38	Single	12 yr.(?)	2 yr.	Simple	6	Slight improvement
16* H. R.	M 23	Single	8 yr.	10 mo.(?)	Simple	17	Marked improvement
17* P. S.	M 25	Married	2 yr.	2 yr.	Hebephrenic	17	Slight improvement
18* G. H.	F 35	Married (twice)	2½ yr.	2½ yr.	Depressed	14	No change
19* V. W.	F 20	Married	7 mo.	4 mo.(?)	Catatonic	22	Marked improvement
20* S. M.	F 37	Married	5 yr.	5 yr.	Undetermined	16	Slight improvement
21* T. C.	F 18	Single	1½ yr.	6 days	Hebephrenic and paranoid	16	Slight improvement
22* L. K.	F 21	Single	5 wk.(?)	3 wk.	Paranoid(?)	10	Marked improvement
23* E. M.	F 30	Single	1½ yr.	3 mo.	Paranoid	7	No change
24* H. T.	M 40	Single	1 yr.	1 yr.	Paranoid	10	Slight improvement
25* G. B.	F 24	Single	2 yr.	6 mo.	Hebephrenic	4	No change
26* A. H.	F 35	Single	22 yr.	1 yr.(?)	Paranoid	7	No change
27† A. L.	F 31	Married	11 yr.	3 days	Hebephrenic	20	Slight improvement
28* E. O.	M 30	Married	2½ yr.	3 mo.	Paranoid	6	Remission

* Twenty-one patients were treated at Minneapolis General Hospital.
† Seven patients were treated at private hospitals.

pitals by staff physicians. Of the 45 patients treated by me, the condition of 28 was diagnosed as schizophrenia. Since patients with schizophrenia often give a history of personality changes (prepsychotic behavior for many months or years) or of previous psychotic episodes, the approximate time of appearance of these manifestations, as well as the time of onset of the present psychosis, is given in table 1. Of the 28 schizophrenic patients, all but 6 showed improvement. Ten showed slight improvement, 7 marked improvement and 5 complete remissions.

TABLE 2.—*Results in Treatment of Affective Disorders with Faradic Shock*

	Case Number and Name	Sex and Age	Marital Status	Previous Attacks	Duration of Present Psychosis	Number of Treatments	Results
Manic-depressive psychoses	29† M. W.	F 44	Single	1st in 1912 (9 attacks)	2 mo.	7	Moderate improvement
Manic type	30* K. M.	F 29	Single	1st in 1937 (2 attacks)	2 mo.(?)	10	No change
	31† J. W.	M 63	Married	1st in 1932 (6 attacks)	1 yr.	13	Slight improvement
Manic-depressive psychoses	32† S. R.	M 58	Married	1st in 1919 (8 attacks)	1 yr.	20	Marked improvement
Depressed type	33† O. A.	F 47	Single	1st in 1932 (2 attacks)	4 mo.	7	Remission (see case report)
	34† L. R.	F 54	Married	1st in 1920	1 yr.	10	No change (see case report)
	35† M. G.	M 55	Married	1st in 1932 (5 attacks)	7 mo.	10	Marked improvement
	36† V. M.	F 53	Single	1st in 1909 (8 attacks)	10 mo.	11	No change
Involutional melancholia	37† F. M.	M 55	Married	None	9 mo.	20	Marked improvement
	38* M. B.	F 44	Single	None	1½ yr.	8	No change

* Two patients were treated at the Minneapolis General Hospital.
† Eight patients were treated at private hospitals.

Five of the patients who showed marked improvement had a relapse (cases 1, 4, 7, 9 and 12). All these 5 patients responded promptly with a second course of treatments; 1 (case 12) had two relapses, but recovered after a third course of treatments. One patient (case 2) failed to improve, but he had previously failed to respond to insulin and metrazol shock treatment. Another (case 8) showed only slight improvement with faradic shock treatment, but a month later recovered after four metrazol treatments. Several workers [11] have observed that patients failing to respond to one form of shock therapy may respond to another.

11. Cook, L. C.: Cardiazol Convulsion Therapy in Schizophrenia, Proc. Roy. Soc. Med. **31**:567-577 (April) 1938. Horwitz, W. A.; Blalock, J. R., and Harris, M. M.: Occurrence of Relapses in Patients Treated with Insulin Hypoglycemic Shock, Psychiatric Quart. **12**:716-721 (Oct.) 1938.

Only 10 patients with affective disorders were treated. This number is obviously too small for any conclusions. Some showed prompt response, although most of the patients treated had chronic conditions (table 2).

The most dramatic results were obtained with faradic shock therapy in 2 cases of acute hysteria. The symptoms promptly subsided with one treatment. Results with the chronic psychoneuroses were far less spectacular (table 3). It appears that favorable results are not obtainable when the personality is partially involved over a long period. After the first few treatments temporary improvement is observed, but most such patients are unable to maintain that level.

TABLE 3.—*Results in Treatment of Psychoneuroses with Faradic Shock*

	Case Number and Name	Sex and Age	Marital Status	First Attack	Duration of Present Episode	Number of Treatments	Results
Hysterical amnesia	39* H. D.	M 29	Married	(?)	4 days	1	Remission (see case report)
Hysterical stupor	40* F. C.	F 20	Single	9 mo.	2 days	1	Remission
Reactive depression	41† E. J.	F 38	Married	20 yr.	18 mo.	14	Slight improvement
	42* C. M.	F 28	Divorced	6 yr.	2 yr.	10	Marked improvement
	43† H. B.	M 49	Married	20 yr.	6 mo.	15	Slight improvement
	44* A. G.	F 39	Married (twice)	12 yr.	9 mo.	8	No change
Hypochondriases	45† R. S.	F 48	Married	15 yr.	5 mo.	10	Slight improvement

* Four patients were treated at the Minneapolis General Hospital.
† Three patients were treated at private hospitals.

Of the first 12 patients to receive a course of less than 15 faradic shock treatments at the St. Peter State Hospital, 8 had had schizophrenia for from six months to two years. Four of the 8 improved, and 3 left the hospital. Four patients with illness of more than two years' duration failed to respond to treatment; 3 of these had severe psychoneuroses of long standing, and the other had a mixed psychosis of six years' duration (probably schizophrenia). At Hastings State Hospital (which receives only patients considered as incurable) 16 patients with chronic schizophrenia of over two years' duration (8 of whom had an illness of over five years' standing) were treated with faradic shock. Five showed improvement, becoming more manageable and cooperative, but none showed sufficient improvement to warrant discharge. Although such results may not appear striking, if some of the chronic schizophrenic patients can be helped in making a better hospital adjustment, the treatment may have merit.

Over one thousand individual treatments have been given to date by me and the medical staffs of two state hospitals without a single serious complication. Sloughing of tissue in the forearm occurred in 1 of the first patients treated (case 3) when a small amount of a 5 per cent solution of pentothal sodium was injected outside the vein, but the lesion healed quickly with the application of hot packs.

It was observed that patients with psychoses of less than six months' duration respond far better than patients with illness of longer standing, and better results were obtained with paranoid and catatonic types than with the hebephrenic and simple types of schizophrenia. The latter conditions usually begin at an early age and more insidiously. Ross and Malzberg [12] reported similar findings in a large group of patients treated with pharmacologic shock therapy in the New York state hospitals.

COMMENT

The chief reason why many physicians do not employ shock therapy is that they believe the possibility of serious complications which may arise from its use is too great. Appreciating the dangers of convulsions induced by drugs, Meduna [13] predicted in 1936: "It will perhaps become possible to eliminate the convulsion and apply only its secondary effects." The electric convulsive therapy is now being introduced as a substitute for metrazol convulsive shock therapy, but whether it is safer has not yet been established.

In all types of shock therapy two conditions are known to occur, namely, (1) physiologic stimulation, followed by (2) depression or temporary inhibition of the higher cerebral centers. I use electricity (faradic current) for stimulation, and intravenous injections of barbiturates for inhibition of the higher cerebral centers. With this procedure faradic shock treatment is under better control and is safer than other present forms of shock therapy.

Although at first Sakel [14] doubted the need of combining psychologic treatment and drug therapy, he later admitted that it is necessary to treat a psychosis "as the expression of a biophysical condition . . . or as a psychobiologic entity in Adolph Meyer's sense." I believe that shock therapy should be considered as treatment by excitation. The sudden introduction of powerful psychologic stimulation from without, it

12. Ross, J. R., and Malzberg, B.: A Review of the Results of the Pharmacological Shock Therapy and Metrazol Convulsive Therapy in New York State, Am. J. Psychiat. **96**:297-316 (Sept.) 1939.

13. Meduna, L.: New Methods of Medical Treatment of Schizophrenia, Arch. Neurol. & Psychiat. **35**:361-363 (Feb.) 1936.

14. Sakel, M., in discussion on Harris, M. M.; Blalock, J. R., and Horwitz, W. A.: Metabolic Studies During Insulin Hypoglycemic Shock Therapy, Arch. Neurol. & Psychiat. **39**:860-863 (April) 1938.

is believed, leads the patient to summon together all his resources and will power to get well, in order to avoid further treatment. Janet [9] advocated that, besides excitation, the physician should use all means possible, such as reeducation and guidance, in the effort to bring about psychologic healing.

Although the number of cases reported in this paper is not large enough for a statistical study, I believe that the results obtained are encouraging. Many of the mental disorders treated were of long standing, and the immediate response to treatment within a few days indicates that the course of the conditions was alleviated or shortened by this method.

The results in the patients treated suggest that faradic shock treatment is as effective as the more drastic forms of shock therapy, but to confirm this a larger series is needed.

CONCLUSIONS

Faradic shock treatment may be considered a psychophysiologic form of therapy. Its chief effect is excitation, but in conjunction with it other forms of psychotherapy, such as explanation, reeducation and guidance, must also be employed.

Seventy-three patients with various mental disorders were treated, with results paralleling those reported with other forms of shock therapy. More striking results were obtained in conditions in which the personality was acutely and more or less totally involved (as in paranoid and catatonic types of schizophrenia) than in conditions in which it was partially involved (as in psychoneuroses) over a long period. Five patients with schizophrenia had relapses after treatment, but all responded quickly with further treatment.

Faradic shock treatment does not produce as profound physiologic changes as other forms of shock therapy in current use, but it can be controlled better, it is safer to use and it is relatively more simple and inexpensive to administer. Its use is recommended before the more drastic forms are tried.

Faradic shock treatment is another means of approach to an intricate problem. It may clarify knowledge as to the proper treatment of psychoses, and it may offer new understanding of the mechanisms involved.

The neuropsychiatric staff of the Minneapolis General Hospital and the staffs of St. Peter, Hastings State and Glenwood Hills Hospitals cooperated and assisted in this work.

CONNECTIONS OF THE RED NUCLEUS

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Connections of the red nucleus are complex and hard to elucidate in histologic series of the normal human brain. The difficulties arise from a number of natural conditions. The nucleus occupies a central position in the tegmentum, where it is closely surrounded by ascending and descending fiber tracts. In man the nucleus consists of three parts, of which the medial and lateral are greatly enlarged, while the large cells of the posterior part are markedly reduced in number.[1] The posterior and lateral parts are traversed by a large mass of fibers of the brachium conjunctivum. Each of the three parts of the red nucleus is related to a descending fiber tract, only one of which, the rubrospinal tract, crosses near its origin. Moreover, the oral end of the red nucleus is enclosed in the prerubral field H, or nucleus campi Foreli, composed of neuropil and cells, which marks the terminus of fibers coming from the pallidum. The cells give rise to a short prerubral tract, which ends in the red nucleus.

Verhaart [2] recently published a paper presenting good experimental and neuropathologic evidence of the connections of the corpus striatum and those of the red nucleus. He expressed the view that direct connections do not exist between the pallidum and the red nucleus and that the corpus striatum may be looked on as regulating through the hypothalamus the vegetative mechanisms of muscle. For this reason he placed undue stress on the connections of the corpus striatum with the hypothalamus. He concluded that although the red nucleus in man is part of the subcortical motor system, its functions are not exercised through the rubrospinal tract as much as through other connections, especially those with the inferior olive and cerebellum.

After analyzing his evidence and examining our own series, we have come to the conclusion that the facts which are presented by his and by

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1. von Monakow, C.: Der rote Kern des Menschen und der Tiere, in Arbeiten aus dem hirnanatomischen Institut in Zürich, Wiesbaden, J. F. Bergmann, 1909, pp. 64-116.

2. Verhaart, W. J. C.: A Comparison Between the Corpus Striatum and the Red Nucleus as Subcortical Centra of the Cerebral Motor System, Psychiat. en neurol. bl. **42**:676-737, 1938.

our material can be harmonized only when the prerubral field H of Forel[3] is included as a link between the pallidal efferent system and the red nucleus. Our purpose is to show that a linked pathway exists from the pallidum through the prerubral field H (nucleus campi Foreli) to the red nucleus, and that a special short prerubral tract connects the prerubral field H with the red nucleus. In addition, we wish to show that the red nucleus emits at least three tracts, the crossed rubrospinal tract, the uncrossed rubroreticulo-olivary tract and the uncrossed rubro-oculomotor tract. The connections, structure and relations of the red nucleus have been illustrated and tersely described by Foix and Nicolesco,[4] whose book may be consulted for general orientation in this region.

MATERIAL AND HISTOLOGIC OBSERVATIONS

Material.—In order to elucidate some of these relations, we have selected a number of series of the human brain stem, each of which demonstrates some of the points listed in the preceding section. The prerubral field H and the connections of Forel's fields H_2 and H_1 can be demonstrated in sagittal and in horizontal series stained by the Weigert method. A series from a 6 month old child shows clearly the segments of the red nucleus and differential myelination of the tracts which pass through the region of the red nucleus. Two transverse series of adult human brains have lesions of the red nucleus from which it is possible to trace three fiber tracts, parts of which have undergone degeneration.

Four Weigert-Nissl series of the brains of primates, the baboon, the mangabey monkey, Macacus rhesus and the chimpanzee, were examined. In these primates the magnocelluiar group of the red nucleus is prominent, and the medial and lateral parvocellular segments are clearly defined, but they are not as large as in man. The prerubral field H is chiefly dorsal to these segments. In the higher anthropoid apes there is a reduction of the magnocellular elements and an increase in the parvocellular segments, conditions which closely approach those seen in man, but the medial (ocular) segment is still small as compared with that in the human brain.

In the brains of lower mammals only the magnocellular group is well defined.[5] The medial and lateral parvocellular segments are so rudimentary as to be readily overlooked. For this reason, the red nucleus and its connections in lower mammals are not well suited for comparison with human material. For example, in the dog the medial, or ocular, segment of the red nucleus is so small that it escapes attention, whereas in the monkey and in man it is well defined.

The diagram in figure 4 was constructed to summarize the connections of the red nucleus as we found them.

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3. Forel, A.: Untersuchungen über die Haubenregion und ihre oberen Verknüpfungen im Gehirne des Menschen und einiger Säugethiere: II, Arch. f. Psychiat. **7**:407-495, 1877.

4. Foix, C., and Nicolesco, J.: Anatomie cérébrale les noyaux gris centraux et la région mésencéphalo-sous-optique, Paris, Masson & Cie, 1925.

5. Davenport, H. A., and Ranson, S. W.: The Red Nucleus and Adjacent Cell Groups: Study in Cat and in Rabbit, Arch. Neurol. & Psychiat. **24**:257-266 (Aug.) 1930.

Sagittal Series N-34-361 and Horizontal Series N-34-361 and N-34-44.— These series were stained by the Weigert method. In these planes of section the descending connections of the pallidum can be clearly demonstrated (figs. 1 *A* and *B*, 2 *A* and 3 *B*). They form the ansa and fasciculus lenticularis. A considerable

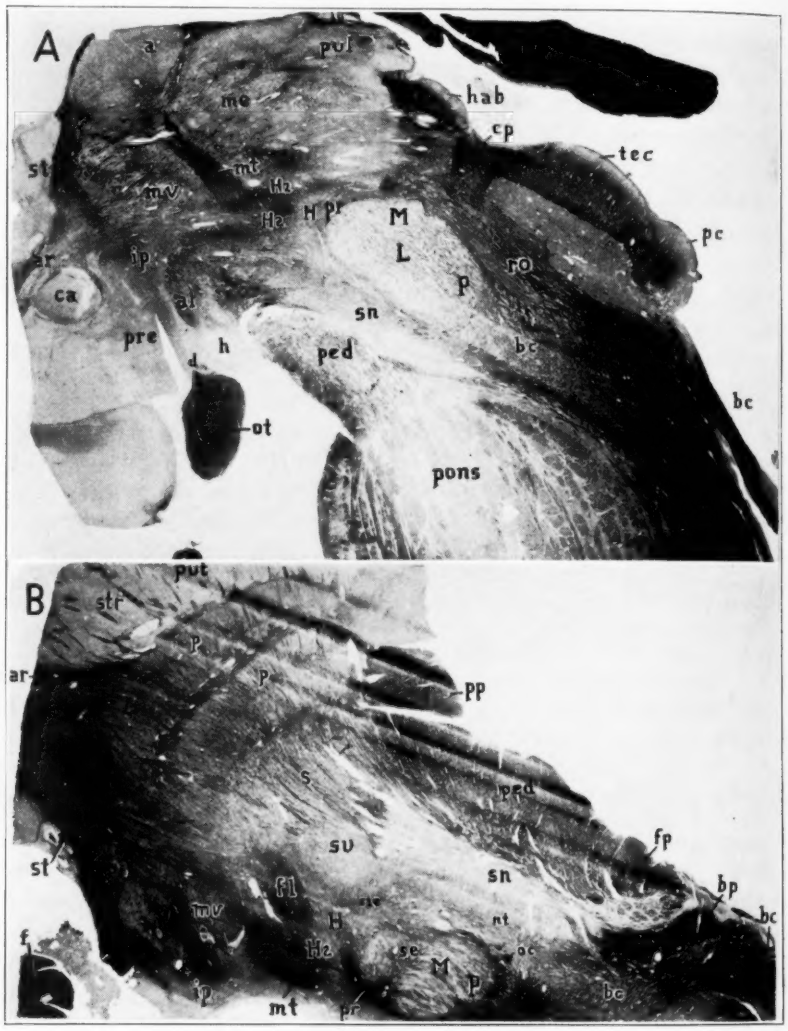

Figure 1

(See legend on opposite page)

part of the fasciculus ends in the subthalamic nucleus (*su*). This nucleus gives origin to the subthalamicotegmental tract (fig. 3 *B*, *ste*), which ends in the lateral tegmental nucleus (nucleus profundus) of the midbrain.[6] From the latter nucleus

6. Papez, J. W.: Reciprocal Connections of the Striatum and Pallidum in the Brain of Pithecus (Macacus) Rhesus, J. Comp. Neurol. **69**:329-349, 1938.

fibers appear to pass down to the inferior olive. This pallidosubthalamicotegmento-olivocerebellar pathway has no direct connection with the red nucleus system which will be described in this paper.

The remainder of the fasciculus lenticularis joins the ansa lenticularis to form Forel's field H_2. This bundle of fibers descends toward the red nucleus and ends abruptly in two ways, in field H_1, and in prerubral field H, or nucleus campi Foreli.

One ending of field H_2 is in the form of diffuse neuropil among cells which surround the oral end of the red nucleus. A few millimeters in front of the red nucleus, Forel's field H_2 presents a blunt end, separated from the red nucleus by a distinct gap, the prerubral field H, or nucleus campi Foreli. It is often assumed that the pallidal efferent fibers which form field H_2 end directly in the red nucleus. That this is not the case was pointed out by Morgan [7] and by Verhaart.[2] This fact can be readily verified in sagittal and horizontal series (figs. 1 *A* and *B*, 2 *A* and 3 *B*).

7. Morgan, L. O.: The Corpus Striatum, Arch. Neurol. & Psychiat. **18**:495-549 (Oct.) 1927.

Explanation of Figure 1

A, parasagittal section through the middle of the red nucleus from series N-34-361. This shows fields H_2 and H and the prerubral tract, *pr*, to the red nucleus. × 2. *B*, horizontal section through the middle of the red nucleus from the other half of the brain in series N-34-361. This shows fields H_2 and H; *fl*; *pr*, the prerubral tract, and *se*, the seam in the red nucleus. × 2.

In this figure and in the accompanying figures, the following abbreviations are used: *a*, anterior nucleus of thalamus; *ac*, acoustic radiation; *al*, ansa lenticularis; *am*, amygdala; *ar*, anterior thalamic radiation; *arc*, arcuate nucleus; *at*, anterior tegmental nucleus; *bc*, brachium conjunctivum; *bic*, brachium of inferior colliculus; *bp*, brachium pontis; *ca*, anterior commissure; *cb*, corticobulbar tract; *cm*, central medial nucleus; *cp*, posterior commissure; *cr*, conjunctival radiation; *cs*, corticospinal tract; *d*, ventral supraoptic decussation; *f*, fornix; *fl*, fasciculus lenticularis; *fp*, frontopontile tract; *h*, hypothalamus; *hab*, habenular region; *hp*, habenulopeduncular tract; *int*, internal capsule; *ip*, inferior thalamic peduncle; *L*, lateral segment of red nucleus; *la*, nucleus lateralis anterior; *le*, lesion; *lg*, lateral geniculate body; *M*, medial segment of red nucleus; *me*, medial nucleus of thalamus; *mb*, mamillary body; *me*, medial nucleus of thalamus; *mg*, medial geniculate body; *ml*, medial lemniscus; *mt*, mamillothalamic tract; *mv*, ventral medial nucleus; *nr*, red nucleus; *nt*, nigrotegmental fibers; *oc*, oculomotor nerve; *on*, oculomotor nucleus; *or*, optic radiation; *ot*, optic tract; *P*, posterior segment of red nucleus; *p*, pallidum; *pc*, posterior colliculus; *pd*, dorsal pulvinar; *ped*, basis pedunculi; *pi*, pulvinar inferior; *pl*, lateral pulvinar; *pp*, parietopontile tract; *pr*, prerubral tract; *pre*, preoptic area; *ps*, pallidosubthalamic tract; *pul*, pulvinar; *put*, putamen; *ro*, rubro-oculomotor tract; *rro*, rubroreticulo-olivary pathway; *rs*, rubrospinal tract; *s*, strionigric fibers; *sn*, substantia nigra; *spt*, spinothalamic tract, or spinobulbothalamic tract; *st*, stria terminalis; *ste*, subthalamicotegmental tract; *str*, striatum; *su*, subthalamic nucleus; *t*, dorsal trigeminal tract; *tec*, optic tectum; *teg*, tegmental nucleus of midbrain or nucleus profundus mesencephali; *v*, pars ventralis of geniculate bodies, and *vp*, ventral posterior nucleus.

The prerubral field H consists of neuropil and cells. It has been called the substantia reticularis hypothalami,[8] the nucleus campi Foreli[9] or the nucleus of fields H and H_2.[10] It can be seen that the neuropil in this field is largely derived from terminals of field H_2, since there is close and visible continuity between them. The experimental degenerations of field H_2 in cats and in monkeys and the pathologic studies of human material support this view. However, a small bundle of fibers from field H_2 runs over the red nucleus to enter the reticular formation, as described by Foix and Nicolesco[4] (see their figure 239), but this is only a minor connection. It is the prerubral field H which appears to make the main connections with the red nucleus. Such a fiber bundle can be readily demonstrated in horizontal series (figs. 1 *B*, 2 *A* and *B* and 3 *B*, *pr*), owing to the fact that the fibers of the prerubral tract run in medially and dorsally. In sagittal sections (fig. 1 *A*, *pr*) the prerubral tract appears as a thin shell of fibers spread over the frontal end of the red nucleus. They enter the red nucleus in part on the surface and in part through the fiber seam (*sc*) which separates the medial and the lateral segment (fig. 2 *A*, *pr* and *sc*).

Field H_2 also curves dorsally close to the mamillothalamic fasciculus (of Vicq d'Azyr) to form the fasciculus thalamicus, or field H_1. This extends laterally and forward under the medial border of the ventral lateral posterior nucleus, in which it ends. This nucleus is a forward extension of the ventral lateral posterior nucleus, in which end the medial lemniscus, the spinothalamic tract and the brachium conjunctivum. It can be shown clearly that the fasciculus thalamicus, or field H_1, is a recurved terminal of field H_2, and that it is separate from the ending of the brachium conjunctivum, which is situated more laterally and posteriorly and is often labeled H_1. There are actually two fiber fields in this region, to which the symbol H_1 has been applied.

There is a flat band of fine fibers which passes ventral to field H_2 and the red nucleus. It ends in the part of the cupuliform formation described by Foix and Nicolesco,[4] which surrounds the ventrolateral surface of the caudal end of the red nucleus. This band of fibers passes dorsal to the substantia nigra and its dorsal fiber zone. It tends to stain brown, and for this reason it can be distinguished from the fiber systems related to the red nucleus and to the substantia nigra. It corresponds to the bundle of fine fibers described by Verhaart[2] (see pages 7 and 17 of his reprint). The fibers appear to be related to the lateral hypothalamic area and may represent a descending visceral pathway. The observations in Verhaart's cases suggest that these fibers actually arise higher up in the nucleus basalis of the corpus striatum. It seems clear that there is a special system of fibers here which passes to the cupuliform formation (*la formatio grise cupuliforme péri-rétro-rubrique*[4]).

Transverse Weigert-Nissl Series of the Brain of a Six Month Old Child.—This series shows the early and strong myelination of the pallidal efferent fibers as they leave the globus pallidus. They stain darkly, and in this respect are in strong contrast with the pale-staining corticopontile and corticospinal tracts which form the

8. Malone, E.: Ueber die Kerne des menschlichen Diencephalon, Berlin, Königliche Akademie der Wissenschaften, 1910.

9. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen des striären Systems, J. f. Psychol. u. Neurol. **25**:627-846, 1920; abstracted, Arch. Neurol. & Psychiat. **10**:563-583 (Nov.) 1923.

10. Papez, J. W., and Aronson, L. R.: Thalamic Nuclei of Pithecus (Macacus) Rhesus: Ventral Thalamus, Arch. Neurol. & Psychiat. **32**:1-26 (July) 1934.

basis pedunculi. The fasciculus lenticularis and ansa lenticularis unite to form the field H_2, which descends to end in the prerubral field H, in front of the red nucleus. This field H consists of fine neuropil, within which are scattered nerve cells collectively known as the nucleus campi Foreli. The majority of fibers from field H_2 end in this field and do not pass beyond to end in the red nucleus.

In this series of a child's brain the prerubral field H was feebly myelinated and could be readily distinguished as a region which separates field H_2 and the red nucleus.

As H_2 approaches the prerubral field H, it gives off fibers which curve dorsally and laterally to form the thalamic fasciculus, or field H_1. Field H_1 rises dorsally along the mamillothalamic tract (of Vicq d'Azyr), which in this and several other series was not myelinated. Under these conditions it becomes evident that field H_1 comes from the end of field H_2. The radiations of the brachium conjunctivum are caudal and lateral to field H_1. Special attention is called to the fact that the medial bundle H_1, the true fasciculus thalamicus, is of pallidal origin, while the lateral bundle is a continuation of the brachium conjunctivum. In the literature they are both designated as field H_1.

The fasciculus thalamicus, or field H_1, ends in the medial border of the ventral nucleus of the thalamus. This nucleus sends fibers into the internal capsule, which pass upward, presumably to the premotor cortex.[11] Thus it can be stated that pallidal efferent fibers end in at least three structures: in the subthalamic nucleus, which connects with the tegmentum of the midbrain; in the prerubral field H, which connects with the red nucleus, and in the ventral lateral nucleus of the thalamus, which connects with area 6 of the cortex.

The red nucleus consists of three segments: the medial, the lateral and the posterior.[1] The medial segment is particularly clear and almost devoid of conjunctival fibers (fig. 2 *B*, *M*). It occupies a medial and dorsal position, close to the medial longitudinal bundle. In transverse sections the segment has a semilunar outline, being separated from the lateral segment by a seam of fibers (*se*). This medial segment gives rise to the uncrossed rubro-oculomotor tract.

The lateral segment is the largest in all dimensions; hence it is often called the *Hauptkern*. It lies along the lateral and ventral side of the medial segment. Its center is traversed by the brachium conjunctivum, which is so compact that the cells are displaced toward the surface. Near its anterior end its dorsal surface presents a slight notch, along which issue the fibers of the rubroreticulo-olivary, or central tegmental, tract.

The posterior magnocellular groups cannot be distinguished topographically from the medial and lateral segments. These groups of large cells are embedded in the surface of the brachium conjunctivum at the level of the oculomotor roots. The few large cells, as well as the smaller cells, of the caudal end of the lateral segment, give rise to the crossed rubrospinal tract.

The medial segment is bordered on its mesial side by a faintly myelinated tract, which extends along the side of the medial longitudinal fasciculus as far down as the nucleus of the trochlear nerve. Beyond this point the tract is much diminished in size, but it may descend as far as the nucleus of the sixth nerve. The vestibular fibers of the medial longitudinal fasciculus and the fibers of the brachium conjunctivum are more heavily myelinated than those of the rubro-oculomotor tract.

11. Walker, A. E.: The Thalamus of the Chimpanzee: IV. Thalamic Projections to the Cerebral Cortex, J. Anat. **73**:37-93, 1938; The Primate Thalamus, Chicago, University of Chicago Press, 1938.

Traced cephalad, the rubro-oculomotor tract fades out at the upper limits of the anterior segment of the red nucleus. Here it is quickly replaced by another tract of fibers (*pr*) from the prerubral field. This second tract (*pr*) is poorly myelinated in the child and seems to consist of short fibers, already described as connecting the nucleus of the prerubral field H with the anterior and lateral segments of the red nucleus. The fibers curve in a horizontal plane around the frontal end of the red nucleus. Since this short tract precedes the rubro-oculomotor tract and occupies a similar position, the question of their continuity naturally arises. The fact that the rubro-oculomotor tract tapers off at the anterior end of the red nucleus before the prerubral tract appears in full volume suggests that the two fiber tracts are in series. The same conclusion may be drawn from Verhaart's experimental series from monkeys.

The lateral segment of the red nucleus (fig. 2 *B*, *L*) is large and rounded in transverse section and is traversed by the well myelinated fiber bundles of the brachium conjunctivum. There is a distinct seam of fibers between the medial and the lateral segment. This seam of fibers (*se*) enlarges anteriorly and blends in part with the fibers of the prerubral tract.

From the interior of the lateral segment of the red nucleus fibers appear to pass dorsally, where they accumulate to form a large tract along the dorsal lateral surface of the red nucleus. This is the large descending rubroreticulo-olivary tract, or the well known central tegmental fasciculus. It is more heavily myelinated than the rubro-oculomotor tract, which lies medial to it, and can be distinguished for a considerable distance in its downward course. Most of it appears to end in the reticular formation caudal to the red nucleus, a cellular region which forms the upper limits for the origin of the reticulospinal tracts. There is also a strong suggestion that a large tract of fibers continues to the inferior olivary nucleus. We cannot say that there is an uninterrupted rubro-olivary tract.

The posterior end of the red nucleus contains on its ventral and lateral side several groups of large cells. These give origin to a small part of the rubrospinal tract. Most of the fibers of this tract come from the small cells of the caudal part of the lateral segment. The rubrospinal tract crosses the midline just in front of the decussation of the brachium conjunctivum and descends in a ventral and lateral position. In contrast to this, the rubro-oculomotor and the rubroreticulo-olivary tracts are homolateral.

Brain Stem Series 87.—M. W., a widow aged 80, was admitted to a hospital three months before her death, suffering from senile psychosis and deterioration. Examination disclosed a spastic condition of the left limbs, with increase in reflexes. There was drooping of the right side of the face. The right pupil was larger than the left, and there was pupillary dysfunction. There were muscular weakness and other signs of senility.

At autopsy, two large lacunar cavities were observed in the right striatum. One involved the head of the caudate nucleus and cut across the frontopontile tract in front of the genu of the internal capsule. The other involved the middle half of the putamen and cut across the corticospinal tract (fig. 3 *A*, *cs*) back of the genu of the internal capsule. The pallidum was not involved by the lesion, but was reduced in size. A complete series of the brain stem was stained by the Weigert method.

Microscopic Examination: The left side was normal. On the right side, there was complete degeneration of the corticospinal and corticobulbar tracts (fig. 3 *A*, *cs*). There was partial degeneration of the most medial part of the frontopontile tract (fig. 3 *A*, *fp*). The strionigric fibers were severely degenerated,

with corresponding reduction in the right substantia nigra reticulata. A large proportion of the cells of the substantia nigra compacta was retained. The ansa lenticularis and fasciculus lenticularis and field H_2, which they formed, were slightly reduced in volume. The subthalamic nucleus and the subthalamicotegmental tract were apparently normal. Field H_2 could be traced to the point where

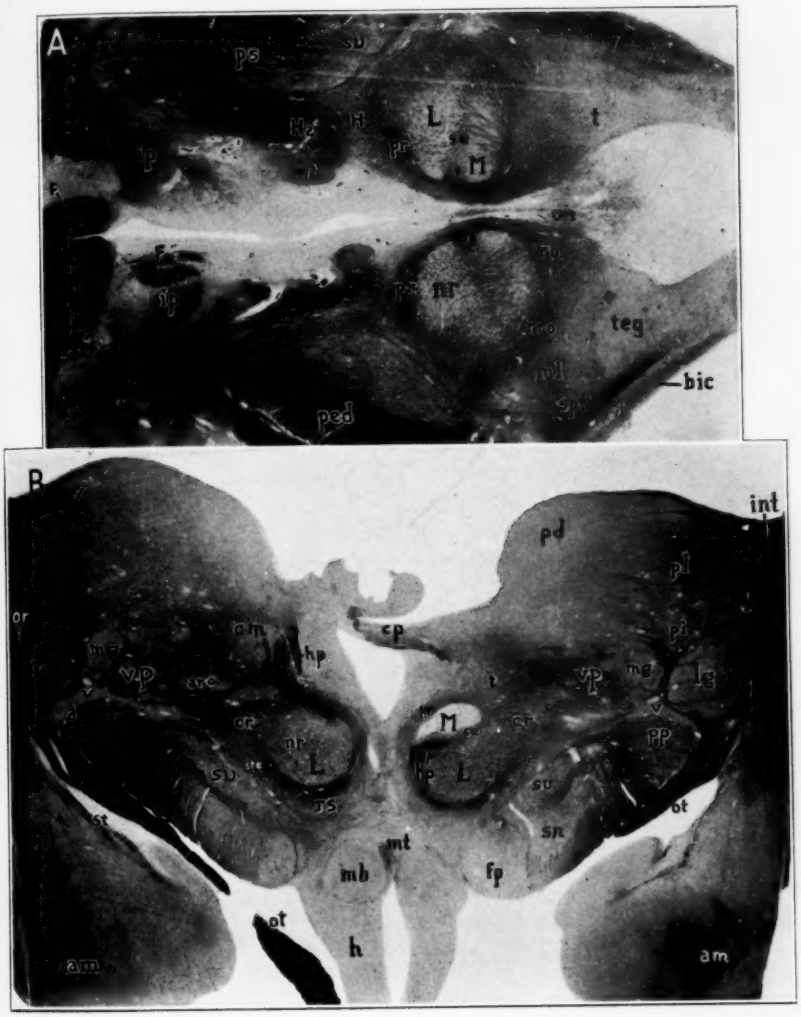

Fig. 2.—*A*, oblique horizontal section from series N-34-44 taken through the middle of the red nuclei. This shows the medial, *M*, and lateral, *L*, segments of the red nucleus; the seam of fibers, *se*, which separates them, and the prerubral tract, *pr*. × 2. *B*, transverse section through the region of the posterior level of the thalamus and of the red nuclei in a 6 month old child. This shows the differential myelination of the basis pedunculi, the fiber tracts related to the red nucleus and the medial, *M*, and lateral, *L*, segments of the red nucleus. × about 2.

it made contact with field H_1, or the thalamic fasciculus. Field H_2 ended also in prerubral field H, in front of the red nucleus.

The nuclei of the dorsal thalamus on the right side were considerably reduced; in particular, the central median nucleus and the medial, the anterior and the ventral lateral nuclei. The pulvinar and the geniculate bodies with their radiations in the posterior limb of the internal capsule appeared better preserved in

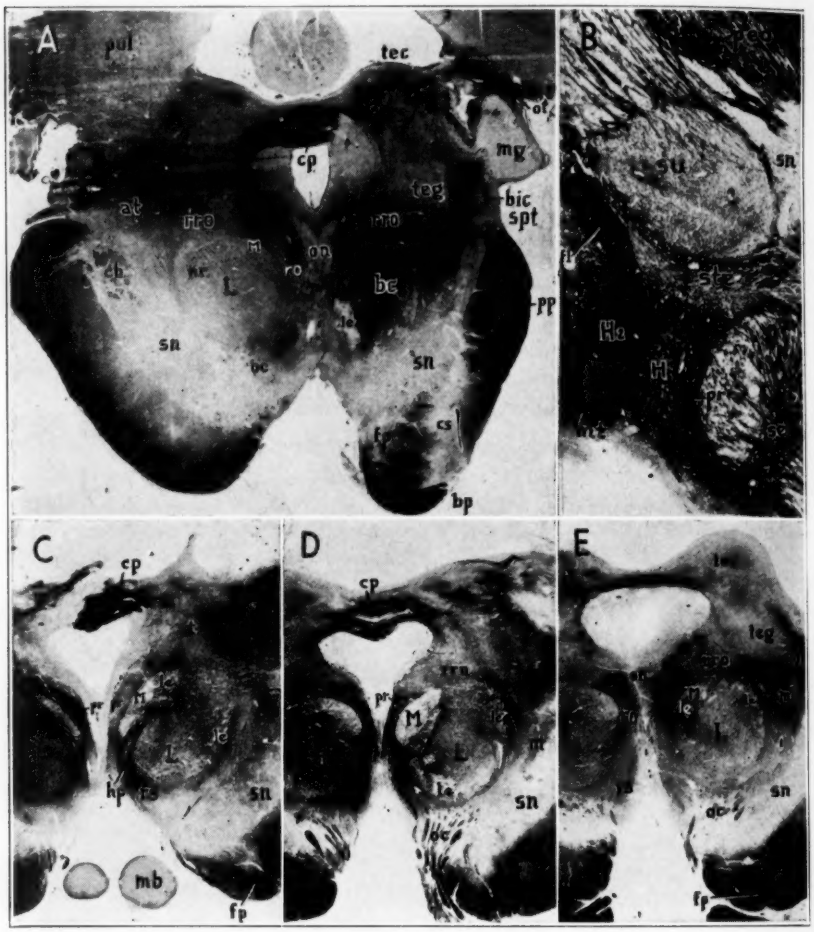

Fig. 3.—*A*, transverse section through the anterior level of the midbrain and middle of the red nucleus in case of M. W., series 87. This shows the lesion, *le*, which caused partial degeneration of the medial segment of the red nucleus and of the rubro-oculomotor tract on the right side. × 2. *B*, horizontal section from series N-34-361, showing the prerubral field *H* (nucleus campi Foreli), the short prerubral tract, *pr*, and the fiber seam, *se*, in the red nucleus. × 2.5.

C, *D* and *E*, three transverse sections through the region of the red nuclei in series in case of J. C. These show the disseminated lesion, *le*, which caused the degeneration of the prerubral tract, *pr*, and partial degeneration of the rubroreticulo-olivary pathway, *rro*, on the right side. × 2.

respect to size and fiber content. The deficiency of the thalamic equipment on the right side was rather outstanding. Such thalamic deficiencies are often seen in brains of persons who have had a major psychosis.

The red nucleus on the right side was much reduced, its medial segment being especially small. There was a distinct small vascular lesion on its mesial side near its posterior end (fig. 3 *A, le*). The lesion was responsible for three evident changes: reduction in the volume of the red nucleus, especially its medial segment; degeneration upward of a part of the brachium conjunctivum, and degeneration of a distinct tract of fibers passing down along the medial longitudinal fasciculus to the nuclei of the third, fourth and sixth nerves.

The reduction of the red nucleus was due to marked shrinkage of its medial segment. The lateral segment was also much shrunken, owing to considerable reduction of the volume of the fibers of the brachium conjunctivum which passed through its interior. The normal as well as the degenerated conjunctival fibers were traced diagonally through the interior of the lateral segment to their radiation into the ventral lateral nucleus of the thalamus.

The descending rubro-oculomotor tract, which was degenerated, came directly out of the lesion in the red nucleus. This tract, represented by a sclerotic streak, curved dorsally to join the medial longitudinal fasciculus on its lateral side. It accompanied the fasciculus to the level of the motor nucleus of the fourth nerve. Beyond this point it was much reduced, but could be traced down to the level of the sixth nucleus as a small diffuse sclerotic streak. The origin of this tract from the shrunken medial segment of the red nucleus seems certain. The dorsal curve of the tract through the medial border of the red nucleus suggested a homology to the cortico-oculomotor tract as illustrated by Dejerine [12] (figure 43, page 201), but we were not able to establish any relation between the degenerated tract and the frontopontile tract. Pretectotegmental fibers which pass from the pretectal nucleus to field H in front of the red nucleus were also degenerated. The deficiency of the pupillary reaction on the right side in this patient is to be noted.

In this case the posterior part of the right red nucleus was normal, and the rubrospinal tracts at their decussation were distinct and equal. The motor functions of this patient were well preserved on both sides, so that she could perform most ordinary movements.

Brain Stem of J. C.—This series of the human brain was described in another connection.[13] A number of small scattered lesions resembling those of multiple sclerosis occurred in the region of prerubral field H and within the red nucleus (fig. 3 *C, D* and *E, le*). These lesions gave rise to degenerations in two fiber tracts.

One small lesion located in the oral end of the medial segment of the red nucleus extended into the prerubral field (fig. 3 *C, le*). As a consequence there was severe demyelination of a short tract situated in front and on the medial side of the medial segment of the red nucleus. Inspection of this demyelinated area indicated that it was a short fiber connection between the prerubral field H and the medial segment of the red nucleus.

12. Dejerine, J.: Sémiologie des affections du système nerveux, Paris, Masson & Cie, 1926.

13. Papez, J. W.: Connections of the Pulvinar, Arch. Neurol. & Psychiat. **41**: 277-289 (Feb.) 1939.

Jakob [14] reported a case (figure 145, page 275 of his volume) in which the pallidum was totally destroyed, with loss of fields H_2 and H_1, but the fibers in prerubral field H were well preserved in relation to the frontal aspect of the red nucleus. Verhaart [2] described a case (figure 21 of his article) in which the fibers of prerubral field H were degenerated without involving field H_2 or field H_1, or the central tegmental bundle. The conclusion from such cases is that a short tract exists between the prerubral field H and the mediodorsal surface and frontal end of the red nucleus.

These were the short fibers degenerated in the case of J. C. (fig. 3 *C*, *pr*). As a result, the medial segment was markedly demyelinated (fig. 3 *D*, *M*). Traced caudally, the fibers quickly disappeared over the mediodorsal surface of the medial segment of the red nucleus. Here a new tract of well myelinated fibers gradually arose and completely replaced the demyelinated tract. This well myelinated tract formed the mediodorsal capsule of the red nucleus and also the outer component of the medial longitudinal fasciculus, with which it was closely associated. Traced downward, this tract appeared to contribute many fibers to the oculomotor and trochlear nuclei. For this reason the fibers were identified as the rubro-oculomotor tract.

The lateral segment of the red nucleus contained an area of scattered lesions resembling those of multiple sclerosis (fig. 3 *D* and *E*, *le*). As a result of the lesion the dorsal fiber field of the red nucleus was partially degenerated. This degeneration was traced into the descending rubroreticulo-olivary tract [15] (central tegmental fasciculus) on the right side (*rro*). Traced downward, this partially degenerated tract mingled with the decussation of the brachium conjunctivum. Below the decussation the tract in question took a mediodorsal position. It appeared that a part of the degenerated tract came into relation with the reticular nucleus situated on each side of the midline caudal to the decussation of the brachium conjunctivum. Caudal to this level the fibers in question joined the dorsal portion of the central tegmental fasciculus, which passed down to the inferior olive.

COMMENT AND CONCLUSIONS

The foregoing data deal largely with the question of pallidorubral connections through the medium of the prerubral field H, or nucleus campi Foreli, with the origin and ending of the fasciculus thalamicus, with the segments of the red nucleus and with the origin and destination of descending rubral tracts. Taken together, these stations and pathways appear to form a descending pallidal system, which is part of the extrapyramidal equipment of the brain stem with cortical, pallidal and cerebellar interconnections.

Another equally important system, descending from the caudate nucleus, the putamen and the substantia nigra to the tegmental nucleus of the midbrain, is not included in this discussion. The subthalamic nucleus

14. Jakob, A.: Die extrapyramidalen Erkrankungen, Berlin, Julius Springer, 1923; The Anatomy, Clinical Syndromes and Physiology of the Extra-Pyramidal System, Arch. Neurol. & Psychiat. **13**:596-620 (May) 1925.

15. Morrison, L. R.: Anatomical Studies of the Central Nervous Systems of Dogs Without Forebrain or Cerebellum, Haarlem, de Erven F. Bohn, 1929; reviewed, Arch. Neurol. & Psychiat. **24**:218-220 (July) 1930.

and its connections are also omitted. The three systems appear to have an olivocerebellar pathway, but the rubral system alone has direct connections with nuclei of motor nerves. The three systems are united by the striopallidal fibers, so some mutual or reciprocal relation must exist between them.

The pallidum receives afferent connections from the medial thalamic nuclei through the inferior thalamic peduncle, as well as the striopallidal fibers. The source of the impulses passing through the medial thalamic nuclei is still undetermined, but diffuse connections from the pulvinar and the ventral lateral and central medial nuclei to the medial nucleus and to the pallidum may be present. On these points knowledge is still deficient. Efferent connections of the pallidum are better known. The ansa lenticularis and the fasciculus lenticularis can be seen arising in the pallidum. After passing around and through the basis pedunculi, they unite to form the descending bundle H_2, which ends abruptly about 2.5 mm. in front of the red nucleus. It has been shown that H_2 does not end directly in the red nucleus, as is often assumed.

The region in front of the red nucleus is occupied by field H of fine myelinated neuropil, within which there are scattered nerve cells. The field is shaped like the bowl of a spoon and encloses the frontal end and mediodorsal surface of the red nucleus. It has been named the substantia reticularis hypothalami, the nucleus campi Foreli and the prerubral field H.

The view supported by the present study is that this prerubral field H is the medium through which field H_2 connects with the red nucleus. The connection consists of short neurons which enter the capsule and seams of the red nucleus. The diagram in figure 4 illustrates this idea. Verhaart's [2] observation on human brains and his experimental results in monkeys can be construed to support this view.

Another structure of importance is the field H_1, often called the fasciculus thalamicus. This bundle appears as an offshoot from the dorsal side of the caudal end of field H_2. It radiates forward and laterally through the medial border and inner part of the ventral lateral nucleus of the thalamus. This is the nucleus ventralis pars ventralis of the monkey.[10] It has been shown by Verhaart [2] that field H_1 degenerates when field H_2 is severed or otherwise affected by lesions of the pallidum, while the cells and short fibers of prerubral field H remain unaltered (*pr* fig. 3 *B*).

There is also clear evidence that field H_1 and the radiations of the brachium conjunctivum are two separate structures, although they occur side by side in the ventral aspect of the ventral lateral nucleus. In addition, there is an intrathalamic bundle associated with the fasciculus thalamicus. The brachium conjunctivum sends fibers also to the central medial nucleus.

The present study supports the view that the fiber bundle H_1, or thalamic fasciculus, is largely a recurved terminal of field H_2 ending in the medial border of the ventral lateral nucleus of the thalamus more anteriorly than the radiations of the brachium conjunctivum. Since the ventral lateral nucleus sends fibers to the motor area or more frontally situated cortex,[11] it is likely that the pallidal discharge influences the cortical field between area 4 and area 6a. Moreover, this premotor cortex sends connections down to the same ventral lateral nucleus of the thalamus. The probability of a "belt line" circuit between the two is at once suggested. If these connections are correct, it follows that impulses coming from the pallidum would generate a two way circuit between the ventral lateral nucleus of the thalamus and the pre-

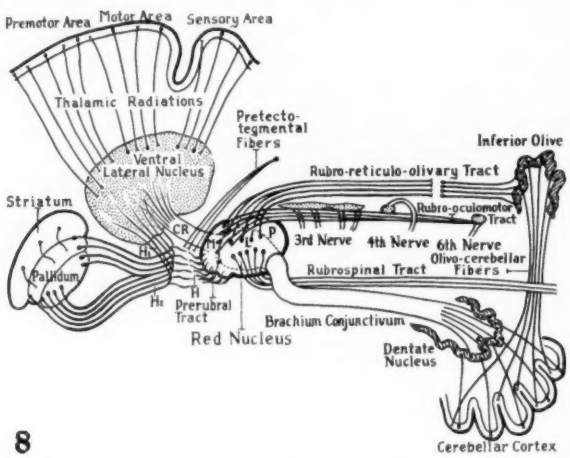

Fig. 4.—Diagram of the connections of the red nucleus in man. This shows the connections of the pallidum with the red nucleus and the premotor area, the connections of the red nucleus with the cerebellum and the rubro-oculomotor and rubrospinal tracts. × 2.

motor cortex at the same time that they excite the functions of the red nucleus. Schuster's [16] studies of lesions of the ventral lateral nucleus of the thalamus in cases of severe motor disorders would support this view. This two way conduction between the thalamus and the motor cortex may have much to do with the progression of the well known march of movement produced by stimulation of the motor area.[17] Any voluntary

16. Schuster, P.: Beiträge zur Pathologie des Thalamus opticus, Arch. f. Psychiat. **105**:358-432 and 550-622, 1936; **106**:13-53, 1936; **106**:201-233, 1937; Berlin, Julius Springer, 1937.

17. Beevor, C. E., and Horsley, V.: A Further Analysis of the So-Called Motor Region of the Cortex Cerebri in the Monkey, Phil. Tr. Roy. Soc., London, s.B **179**:205-256, 1888.

activity arising in the cortex would set into operation at the same time impulses along the corticospinal tracts and the motor nuclei and a discharge by way of the corticopontocerebellodentorubrothalamocortical circuit.

The functional role of the red nucleus in this motor nexus may be surmised from its descending connections. In order of their length these are: the rubro-oculomotor tract, the rubroreticulo-olivocerebellar pathway and the rubrospinal tract. The last is a crossed tract which probably ends in relation to motor cells in the cord.

The rubro-oculomotor tract comes from the medial segment of the red nucleus and follows closely along the medial longitudinal fasciculus. It forms most of the mediodorsal capsule of the red nucleus caudal to the short prerubral tract. In its course it contributes many fibers to the oculomotor and trochlear nuclei. Below the trochlear nucleus it becomes reduced in size, but there are indications that a small part reaches the nucleus of the sixth nerve. If these facts are correct, the inference is that a part of the red nucleus regulates movements of the eye muscles. Ogawa [17a] described in the cat a tractus tegmenti medialis in this position which connects with the inferior olive.

The presence of pretectotegmental fibers, which pass from the pretectal region to the front of the red nucleus, contributes to this view.[18] These fibers arise in the pretectal nuclei and end in the prerubral field or directly in the medial segment of the red nucleus. No one has attempted to explain the presence of these fibers. We suggest that they may have something to do with tectal innervation of the medial segment of the red nucleus, and hence of the ocular nerves. The pretectal nuclei are rudimentary in man, but conspicuous in lower mammals.

The rubrospinal tract arises from the caudal parts of the lateral segment of the red nucleus. The large cells, which are few, also contribute to this tract. There are indications that in the primate brain the rubrospinal tract may be reduced in size and in functional importance. It crosses the midline at the caudal end of the red nucleus and descends in a lateral position close to the motor nuclei of the fifth, seventh, tenth and eleventh cranial nerves, and in the spinal cord along the ventral aspect of the crossed corticospinal tract. It is probably not safe to assume that the rubrospinal tracts are rudimentary and functionless in man.[2] In the case of M. W., series 87, the motor functions and the rubrospinal tract were well preserved on the left side in spite of total loss of the corticospinal tracts.

17a. Ogawa, T.: The Tractus Tegmenti Medialis and Its Connection with the Inferior Olive in the Cat, J. Comp. Neurol. **70**:181-190, 1939.

18. Papez, J. W.: Superior Colliculi and Their Fiber Connections in the Rat, J. Comp. Neurol. **51**:409-439, 1930.

The rubroreticulo-olivary tract is one of the largest tracts in the human brain stem. It issues from the dorsal side of the large lateral segment of the red nucleus. It is a component of the well known central tegmental fasciculus, or thalamo-olivary tract. It descends through the reticular formation, where it appears to make connections with the reticular nuclei which give origin to the reticulospinal tracts. However, the main connection of this pathyway is probably with the inferior olive. The view presented here is that the lateral segment of the red nucleus propagates excitations to the cerebellum through the rubroreticulo-olivocerebellar pathway, and that this flow of impulses is accessory, or reciprocal, to those which flow along other pathways of voluntary action, such as the corticostrionigrotegmento-olivocerebellar pathway.

The conclusions are that the red nucleus occupies a central position in the tegmentum, connected on the one hand with the pallidum and on the other with the oculomotor centers and the motor nuclei of the spinal cord, and that, in addition, it has a separate pathway through the inferior olive to the cerebellum. This does not exclude the possibility of a rubroreticulospinal connection with motor nuclei of the spinal cord.

Theory of Reciprocal Innervation of the Motor Apparatus Through the Corpus Striatum and Cerebellum.—It seems that such a maze of central pathways calls for the formulation of some theory of function. The pathways to the cerebellum are usually double, one of the pair passing through the inferior olive. Examples of such paired tracts are: the spinocerebellar and the spino-olivocerebellar; the corticopontocerebellar and the corticostrionigrotegmento-olivocerebellar; the pallidosubthalamicotegmento-olivocerebellar and the pallidorubroreticulo-olivocerebellar, and the tectopontocerebellar [17] and the tectotegmento-olivocerebellar. The vestibulocerebellar connections furnish another example of this multiple afferent innervation of the cerebellar cortex.[19] It is suggested here that the dual afferent supply of the cerebellar cortex mediates a reciprocal discharge,[6] and that various areas of the cerebellar cortex can be alternately excited or inhibited in connection with reciprocal innervation of the muscles. The Purkinje cells of the cerebellar cortex receive the climbing fibers, and the granule cells receive the mossy fibers. It is quite possible that excitation and inhibition [20] take place concomitantly in different areas of the cerebellar cortex, and hence elsewhere along the motor pathways.

Although the functional meaning of the red nucleus is by no means clear, the concept of a reciprocating innervation mediated by the corpus

19. Larsell, O.: The Cerebellum: A Review and Interpretation, Arch. Neurol. & Psychiat. **38**:580-607 (Sept.) 1937.

20. Miller, F. R., and Banting, F. G.: Observations on Cerebellar Stimulation, Brain **45**:104-112, 1922.

striatum and the cerebellar cortex does make sense out of a maze of stations and tracts which deal with the motor functions. It seems likely that between the corpus striatum and the cerebellar cortex there exist duplex pathways through the red nucleus and through the substantia nigra and tegmentum which facilitate reciprocal innervation of the muscular apparatus. To this smooth, biphasic innervation the terms coordination and synergy are often applied. The pallidum and the red nucleus are regarded as stations in one of these important mechanisms of central motor control.

"SPINAL DYSRAPHISM"

SPINA BIFIDA AND MYELODYSPLASIA

BEN W. LICHTENSTEIN, M.D.
CHICAGO

Since 1641, when Tulpuis [1] described a curious malformation of the spinal cord and the meninges to which he gave the name spina bifida, the medical literature has been replete with clinical, embryologic and pathologic reports of this condition. Despite the outstanding studies of von Recklinghausen [2] and the extensive works of Denucé,[3] Hesse,[4] Sternberg,[5] Leveuf [6] and others, studies of conditions related to, or part of, spina bifida in the larger sense continue to appear in the medical literature, with the lesion masquerading under a variety of terms. Since spina bifida is primarily an expression of inadequate or improper fusion of the embryonal tissues in the dorsal median region of the developing embryo, the resultant pathologic states will be manifested in the cutaneous, mesodermal or neural derivatives of these tissues. This defective fusion of tissues has been adequately designated by the term dysraphism, or status dysraphicus (Henneberg, cited by Bremer [7]). Severe forms of the dysraphic disorder, or rachischisis, are common and of no particular clinical interest. It is in cases in which the dysraphic state is manifested solely in the spinal cord that I am particulary interested, as the absence of clinical and roentgenographic evidence of a vertebral defect may lead the clinician to exclude the possibility of such a disorder of the spinal cord. With particular attention to the spinal cord, I have selected 3 cases illustrating many of the characteristic anomalies of the spinal cord belonging to the spina bifida, or dysraphic, group.

Read at a meeting of the Chicago Neurological Society, Jan. 18, 1940.

From the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine.

1. Tulpuis, cited by Leveuf.[6]

2. von Recklinghausen, F.: Untersuchungen über die Spina bifida, Virchows Arch. f. path. Anat. **105**:243, 1886.

3. Denucé, M.: Spina bifida. Anatomie, pathologie et embryogénie, Paris, O. Doin, 1906.

4. Hesse, F. A.: Spina bifida cystica, Ergebn. d. Chir. u. Orthop. **10**:1197, 1918.

5. Sternberg, H.: Ueber Spaltbildungen des Medullarrohrs bei jungen menschlichen Embryonen, ein Beitrag zur Entstehung der Anencephalie und der Rachischisis, Virchows Arch. f. path. Anat. **272**:325, 1929.

6. Leveuf, J.: Etudes sur le spina bifida, Paris, Masson & Cie, 1937.

7. Bremer, F. W.: Klinische Untersuchungen zur Aetiologie der Syringomyelie der Status dysraphicus, Deutsche Ztschr. f. Nervenh. **95**:1, 1926.

REPORT OF CASES

CASE 1.—A white girl aged 5½ weeks, with a mass in the lumbosacral region, was admitted to the Cook County Hospital. From the mother it was learned that the child was delivered spontaneously and weighed 5 pounds (2,268 Gm.) at

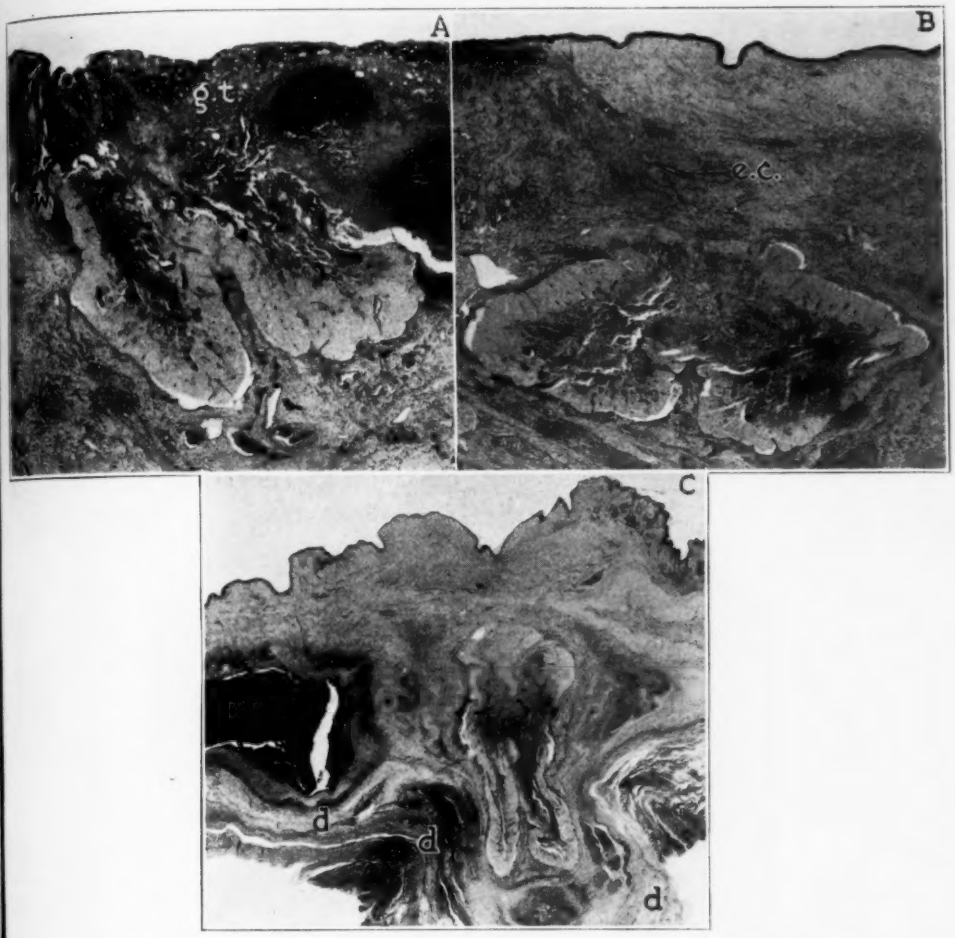

Fig. 1.—Low power photomicrographs of transverse sections through the lumbar region of the spinal cord. In *A* the region usually occupied by the dorsal columns is the site of a vascular granulation tissue (*g.t.*), which fuses with a similar tissue in the subcutis; *w* indicates the island of aberrant white substance of the spinal cord. In *B* the cutis is atrophic, and dorsal to the spinal cord is an ectopic canal (*e.c.*) lined with ependyma. *C* shows the dura (*d*) extending laterally into the subcutis. Van Gieson stain.

birth. The lumbosacral mass was noticed at the time of delivery. Other than the aforementioned mass, the essential physical finding was flaccid paralysis of both lower extremities. Despite aseptic care, the skin over the lumbosacral protrusion

became macerated and infected, and the child died of leptomeningitis shortly afterward. The anatomic diagnosis was rachischisis, myelodysplasia, dural araphia and suppurative leptomeningitis.

Except for the profound defect of the dorsal arch of the vertebral neural canal in the lumbosacral region, the essential findings were restricted to the spinal cord and its meninges.

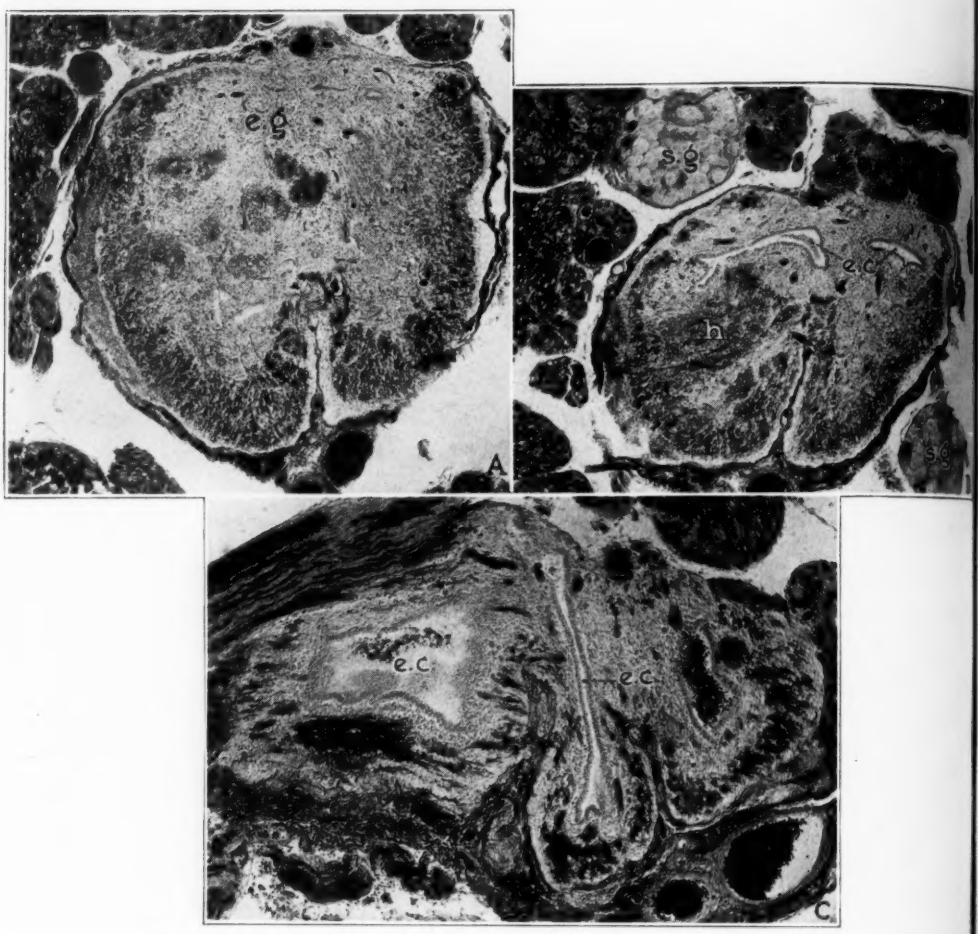

Fig. 2.—Low power photomicrographs of transverse sections through the lower lumbar and the upper sacral level of the spinal cord. *A* shows the dorsal median region of the spinal cord to be the site of hyperplasia of ependymal tissue; *e.g.* represents ependymal glia. In *B* are shown extensive hemorrhages (*h*) in the glia; *e.c.* indicates ependymal canals and *s.g.* spinal ganglia. *C* shows multiple (three) canals (*e.c.*) lined with ependyma. Kultschitzky-Pal preparations counterstained by the Van Gieson method.

Microscopic Observations on the Spinal Cord.—In the cervical and thoracic segments the configuration of the spinal cord was normal and the leptomeninges were

infiltrated with large numbers of polymorphonuclear leukocytes. The lumbosacral segments of the spinal cord were just beneath the cutis (fig. 1). The epidermis in places was superficially ulcerated and was the site of vascular granulation tissue. The pia-arachnoid was markedly hyperplastic, and the dura mater, which ventrally and laterally appeared normal, was not present dorsally to close over the spinal cord but extended laterally and fused with the connective tissue of the subcutis. Whereas the anterior columns of the spinal cord in these levels appeared normal, the dorsal half of the spinal cord was the site of a vascular granulation tissue which fused with a similar tissue in the cutis (fig. 1*A*). This granulation tissue invaded and replaced the gray substance; only occasional ganglion cells were seen, and these showed marked regressive changes. The granulation tissue was rich in polymorphonuclear leukocytes, and in some places sharply defined abscesses were present. In the fibrous tissue beneath the cutis, lateral to the spinal cord, there were islands of aberrant white substance of the spinal cord. At an adjacent level the spinal cord was enveloped in dense fibrous connective tissue, and dorsal to it were islands of aberrant white substance and an ectopic canal lined with ependyma (fig. 1*B*). At other levels the spinal cord was divided into two parts by a downgrowth of fibrous connective tissue in the dorsal median septal region.

The pathologic changes may be summarized as follows: cutaneous defect in the lumbosacral region, with rachischisis, nonfusion of the dura mater dorsally (dural araphia) and maldevelopment of the spinal cord; islands of aberrant white substance of the spinal cord and canals lined with ependyma in the connective tissue dorsal to the spinal cord, and pseudoduplication of the spinal cord at one level—in short, cutaneous, mesodermal and neural dysraphia.

Case 2.—A white boy aged 5 years was admitted to the Cook County Hospital complaining of abdominal pains, nausea and vomiting, of five hours' duration. The essential findings were a temperature of 104 F. and harsh breath sounds throughout the lungs. Weakness of the cervical muscles was noted. A diagnosis of preparalytic poliomyelitis was made, which was later changed to one of acute bacillary dysentery. The child died the day after his entrance to the hospital. Because of the diagnosis of poliomyelitis the spinal cord was removed. The vertebral spines were normal throughout, as were the vertebral neural canal and the dura mater. Outstanding changes were found in the spinal cord.

Microscopic Observations on the Spinal Cord.—Sections stained by the Kultschitzky-Pal method and counterstained by the Van Gieson technic showed severe alteration of the internal configuration of the spinal cord at the sacral levels. The changes were restricted for the most part to the region of the central canal and the area dorsal to it. Whereas the lower lumbar levels showed normal-appearing myelinated nerve fibers in the posterior columns and a sharply circumscribed group of glia cells surrounding a small central canal, at the sacral levels the region behind the white commissure and between the two posterior gray horns showed marked diminution in the number of myelinated nerve fibers (fig. 2). Throughout this poorly myelinated area were large numbers of loosely packed cuboidal to polygonal cells with ample cytoplasm and sharply defined, deeply staining nuclei rich in chromatin. Within these cellular aggregates were well formed and clearly defined central canal formations, lined by a single layer of high

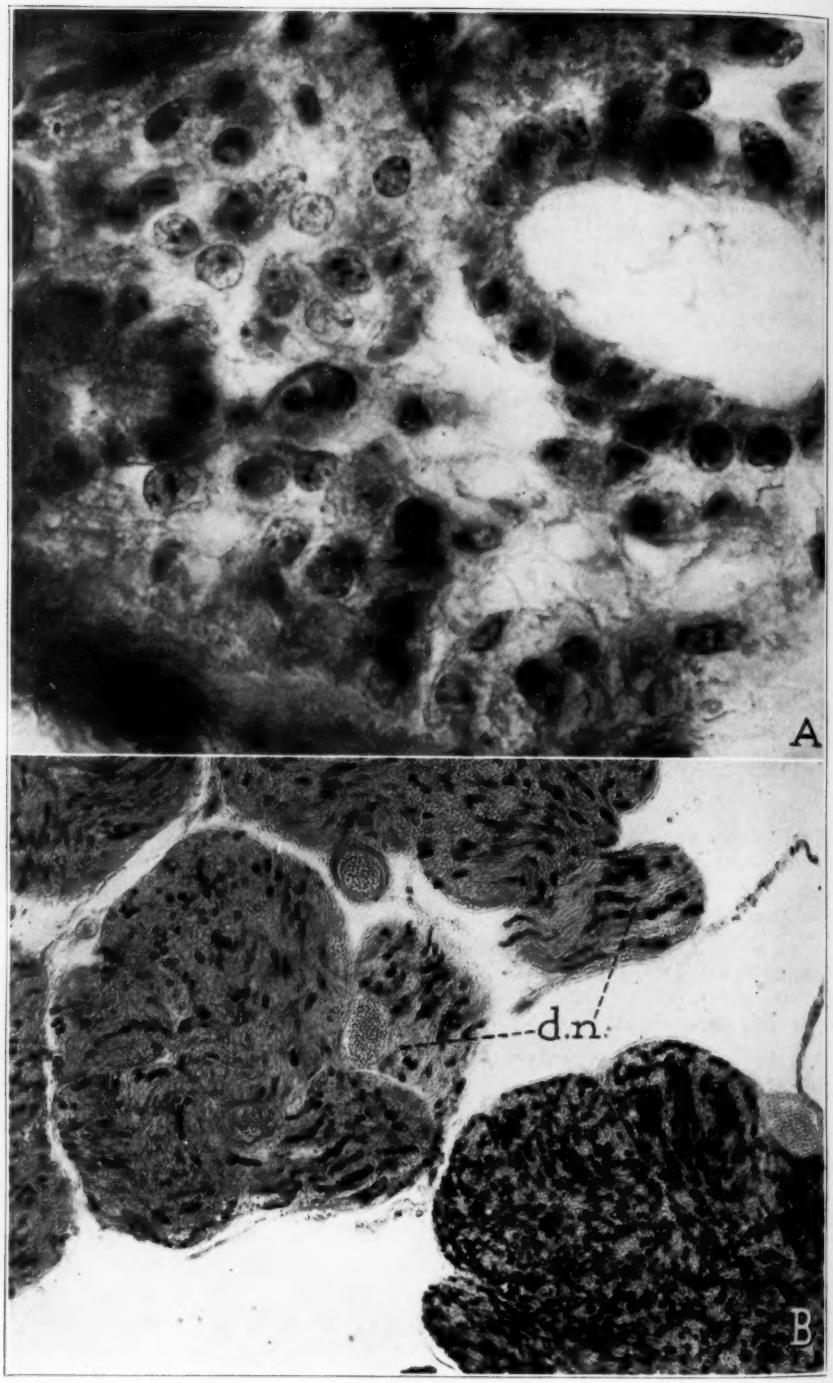

Figure 3

(See legend on opposite page)

columnar ependymal epithelium (fig. 3*A*). From two to three central canals were present at some of the sacral levels, and these structures varied considerably in shape, being elongated and branching and having clear central lumens (fig. 2*B* and *C*). At some levels the enlarged central canals, with their subjacent accumulations of glia cells, had invaded and destroyed a greater part of the lateral and anterior gray columns. These glial accumulations were rich in dilated and engorged capillary blood vessels, and scattered throughout were focal and confluent extravasations of red blood cells, which in some places were seen within the lumens of the central canals (fig. 4*A*). The nerve fibers enmeshed in these hemorrhagic extravasations showed fenestrations and budlike swellings of their myelin sheaths (fig. 4*B*). Where the hemorrhages and glial accumulations penetrated into the anterior horns, the large motor ganglion cells and the interlacing nerve fibers were decreased in number. In places the hemorrhagic extravasations had broken through the marginal glial layer and had separated it from the underlying pia for a considerable distance. Among the recent hemorrhages was evidence of older ones in the presence of large mononuclear cells filled with golden brown pigment material.

Whereas the spinal nerve roots arising from the cervical and the thoracolumbar portion of the spinal cord were normal in appearance, those from the regions of the conus and epiconus showed marked degeneration (fig. 3*B*). The degeneration, though present in the anterior as well as in the posterior nerve roots, was more marked in the latter.

The pia in the sacral regions was hyperplastic, but the arachnoid and dura were for the most part unchanged. At many levels miniature spinal ganglia were seen in the subarachnoid space subjacent to the spinal cord (figs. 2*B* and 4*A*). These ganglia were enveloped by layers of hyperplastic connective tissue, and their internal structure appeared unchanged.

The pathologic changes may be summarized as follows: hyperplasia of ependymal cells with multiple atypical central canal formations in the region of the dorsal median septum at the sacral level of the spinal cord; extension of the ependymal glial tissue into the gray substance; marked capillary stasis and hemorrhagic extravasations throughout this area, with destruction of many of the subjacent nerve fibers and ganglionic cell groups; degeneration of some of the anterior and many of the posterior spinal nerve roots at this level; ectopia of the sacral spinal ganglia, with their localization in the spinal subarachnoid space—in short, neural dysraphia without evidence of a cutaneous or vertebral defect.

CASE 3.—The patient was a white boy 20 days old at the time of death. The child was born of the mother's tenth pregnancy. The other children were living and well, and there was no familial history of spina bifida. At birth a large soft swelling, about the size of a lemon, was present in the lumbosacral region of

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EXPLANATION OF FIGURE 3

A, is a high power photomicrograph of the canals lined with ependyma which were shown in figure 2; they are seen to be surrounded by ependymal glia. Mallory's phosphotungstic acid hematoxylin stain. *B* shows the contrast between the degenerated roots (*dn*) and the normal roots (discussed in the text). Kultschitzky-Pal stain.

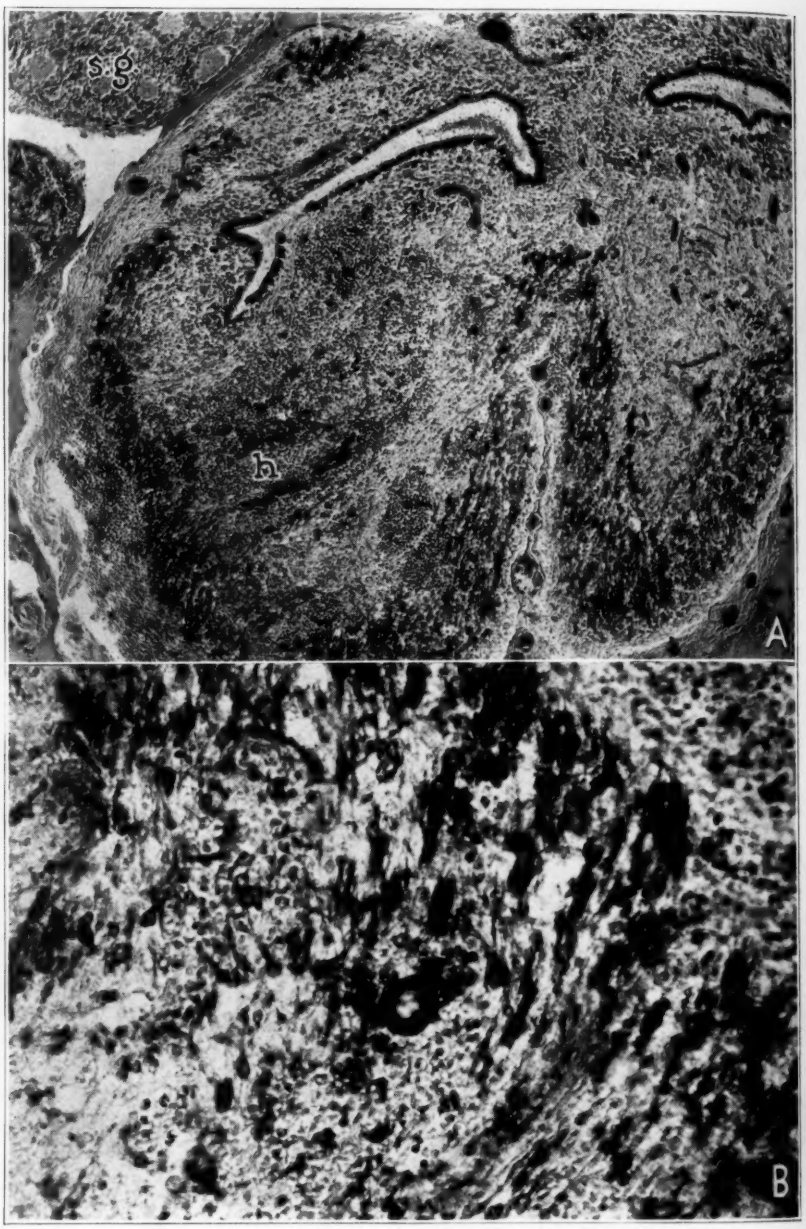

Fig. 4.—*A*, a higher power photomicrograph of the section in figure 2, *B*, shows the ectopic spinal ganglia (*s.g.*) and the hemorrhages (*h*) in the ependymal glia. Kultschitzky-Pal preparation counterstained by the Van Gieson method. *B*, a higher power photomicrograph of area *h* in *A*, shows the swollen myelinated nerve fibers separated by extravasation of red blood cells. Kultschitzky-Pal stain.

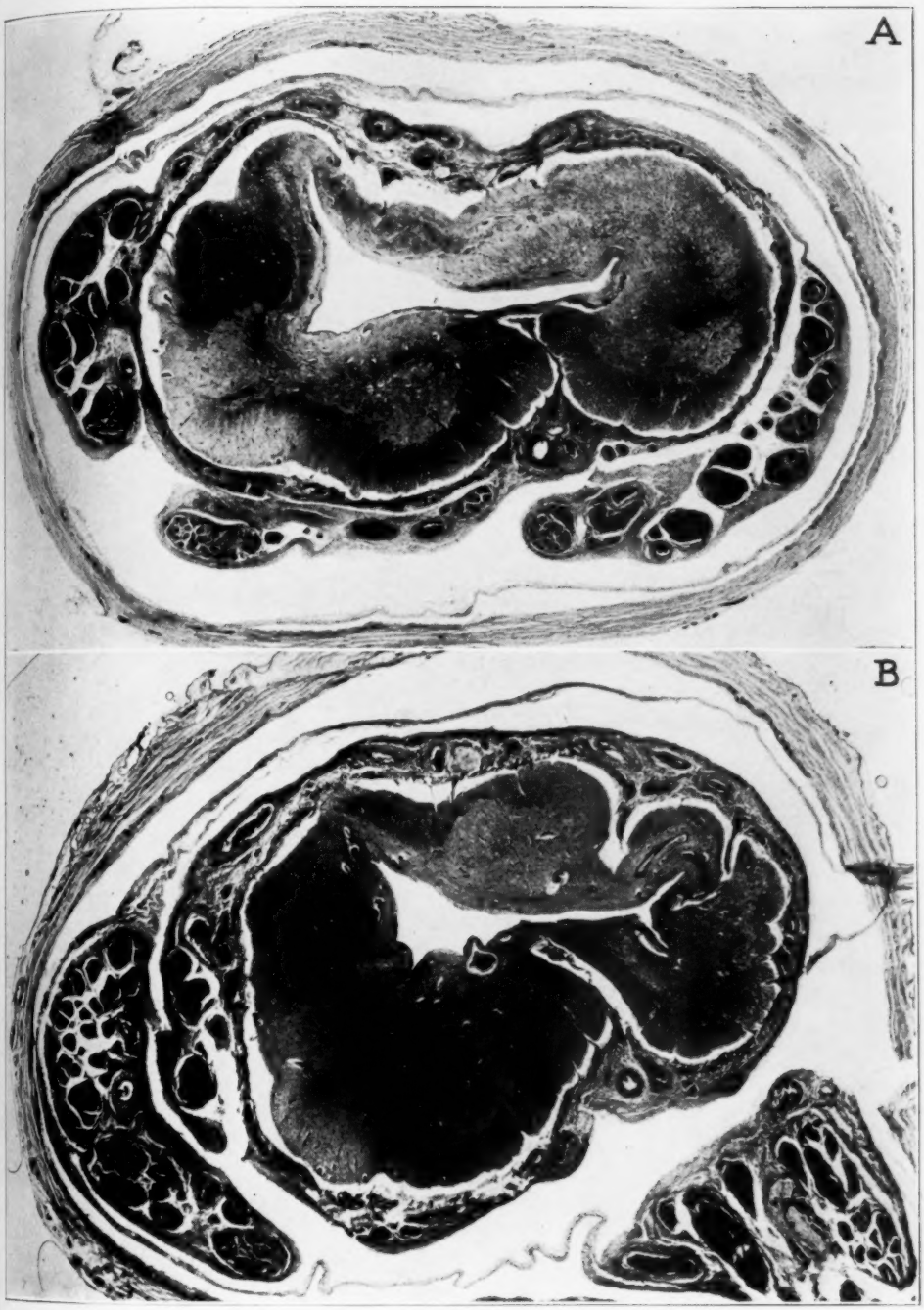

Fig. 5.—Low power photomicrograph through the upper lumbar segments of the spinal cord. *A*, marked hydromyelia; *B*, hydromyelia and beginning duplication. Kultschitzky-Pal preparation counterstained by Van Gieson method.

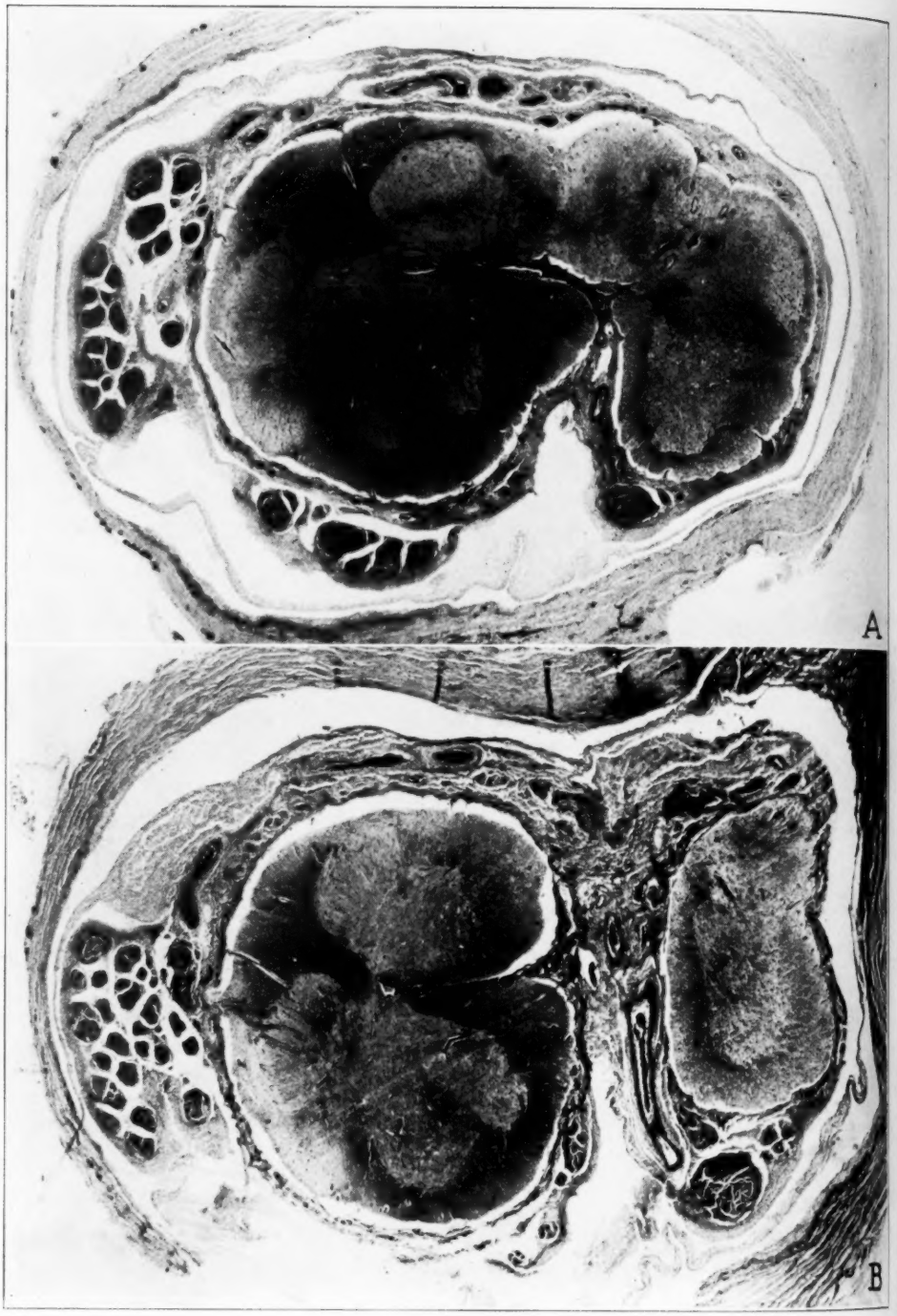

Fig. 6.—Low power photomicrographs through the lower lumbar segments of the spinal cord. *A*, partial separation of the spinal cord into two segments; *B*, complete separation. Same stain as that in figure 5.

the spine. There was a defect in its central portion from which clear fluid was discharging. Soon afterward the tissues about the defect became infected and the temperature rose to 104 F. Smears from the defect in the skin showed gram-positive cocci in short and long chains.

The anatomic diagnosis was: purulent leptomeningitis, spina bifida lumbosacralis with myelodysplasia, cloudy swelling of the liver and septic softening of the spleen.

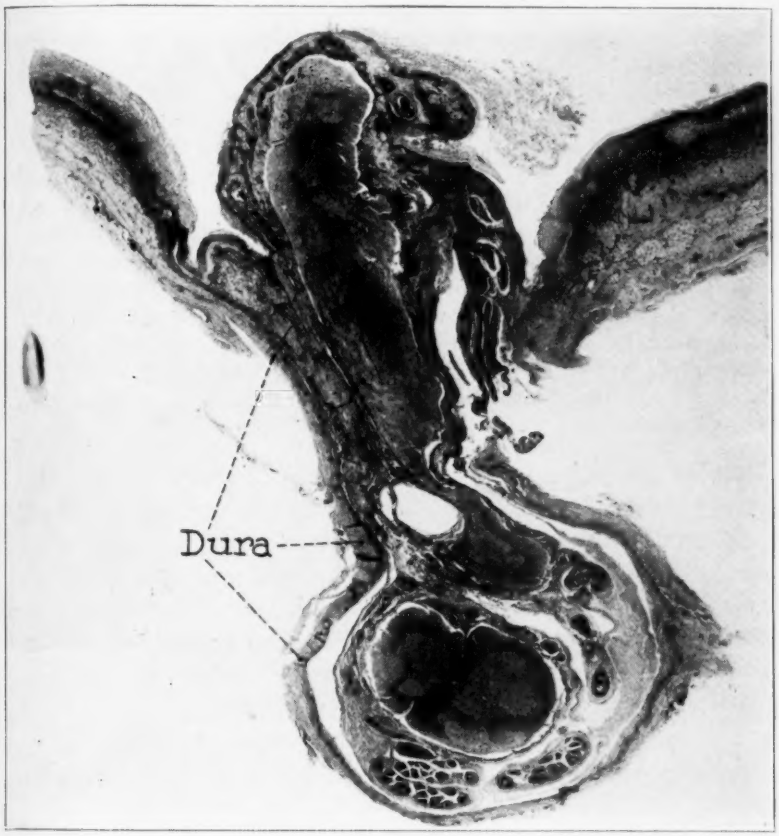

Fig. 7.—Lower power photomicrograph at the site of pseudoduplication of the spinal cord. One segment extends into the meningocele sac. The dura extends laterally into the subcutis. Same stain as that in figures 5 and 6.

Microscopic Observations on the Spinal Cord.—Sections through various levels of the spinal cord showed the leptomeninges to be infiltrated by large numbers of polymorphonuclear leukocytes, small round cells and large mononuclear cells. These infiltrations were most marked about the pial blood vessels and the emerging spinal nerve roots. The internal configuration of the spinal cord in the cervical segments was unchanged. Beginning in the upper thoracic levels, and extending

downward to the lumbar levels, the central canal became progressively larger. In the upper lumbar segments the enlarged central canal distorted the internal configuration of the spinal cord considerably, and a diverticulum-like outpouching extended on one side into Goll's column, almost reaching the pial-glial membrane posteriorly (fig. 5*A*). In more caudal segments the alterations in the size and configuration of the central canal became more marked. At first unequal division occurred, with the formation of two central canals at some levels. In these segments the separation of the spinal cord into two unequal portions was beginning to manifest itself (fig. 5*B*). At lower levels the anterior median fissure became deeper, and at the points where branches of the anterior spinal artery penetrated the substance of the spinal cord, connective tissue prolongations of the pia extended into both halves of the spinal cord, producing secondary anterior fissures. The region posterior to the anterior median fissure was the site of one of the posterior horns (fig. 6*A*). At still lower levels the division of the spinal cord into two portions was completed. The larger of these two portions contained one large anterior and one large posterior horn as well as part of a second posterior horn (fig. 6*B*). The smaller segment contained three central canal formations at some levels, which on serial section were seen to be diverticula of the main central canal. Further caudally the posterior portion of the smaller half of the spinal cord was elongated and extended dorsally into a meningocele sac (fig. 7). The central canals, as well as their diverticulum-like outpouchings, were everywhere surrounded by a zone of glial tissue. In the areas containing several central canals the subjacent subependymal tissue fused to form larger irregular areas of so-called gliosis.

The pathologic changes may be summarized as follows: hydromyelia in the thoracolumbar segments of the spinal cord and separation of the central canal into two branches; diastasis of the spinal cord into two completely separated portions, i. e., diastematomyelia; secondary diverticulum-like outpouchings from the central canal, with multiple atypical central canal formations, and fusion of the subependymal gray substance into irregular areas of so-called primary ependymal gliosis.

PATHOLOGIC CONSIDERATIONS

From the histologic study of the cases presented it is evident that the structures involved in spina bifida may be the neural, mesodermal and cutaneous derivatives of the embryonal tissues in the dorsal median region of the embryo. Some of the pathologic states resulting from such defective fusion are noted in the accompanying table.

Cutaneous and Mesodermal Defects.—As the interest here concerns particularly the anomalies of the spinal cord, a few lines will suffice for the cutaneous and mesodermal defects. Of the cutaneous dysplasias belonging to the dysraphic group, a defect in the skin over the bony defect is the most striking. Other cutaneous dysplasias not uncommonly seen are: localized hypertrichosis; hypoplasia of the skin, with the

absence of hair follicles and sweat glands; dermoid cysts; pilonidal cysts, and the so-called congenital dermal sinuses.[8]

Of the mesodermal dysplasias, the foremost are the bone defects. These may vary considerably in degree from mere splitting of the terminal portion of the vertebral spine to complete absence of the spine or from a defect to the complete absence of the dorsal arch of the vertebral neural canal. Associated with failure in proper closure of the vertebral neural canal there may be dural dysraphia, in which the dura mater does not adequately close dorsal to the spinal cord. Nonclosure of the vertebral neural canal and dural dysraphia are, I believe, the sine qua non of meningocele formation. Among the minor types of mesodermal dysplasia may be mentioned the occasional abnormal accumulation of fat tissue at the site of a vertebral defect.

Spina Bifida, Spinal Dysraphism or the Spinal Dysraphic State

Embryonal Origin	Type of Dysplasia	Resultant Condition
Cutaneous; somatic ectodermal	Cutaneous	Cutaneous defect Hypertrichosis Hypoplasia of skin Pilonidal cysts Congenital dermal sinuses
Mesodermal	Vertebral	Absence of spinous process Split spinous process Cleft in vertebral neural arch Rachischisis
	Dural	Nonfusion of dura mater
Neural; neurectodermal	Neural tube	Myelodysplasia Intramedullary and extramedullary growths associated with dysraphia
	Neural crest	Ectopia of spinal ganglia

Neural Defects.—The neural dysplasias belonging to the spina bifida group are anomalies of the spinal cord and its ganglia. Some of the anomalies of the spinal cord associated with the dysraphic state are diagrammatically illustrated in figure 8.

Araphia: This is the most primitive form of myelodysplasia. Owing to nonclosure of the neural tube, the spinal cord develops as a flat plate (fig. 8). The developing anterior median fissure may divide the spinal cord into halves. In such cases there is no central canal and many of the ependymal cells which lie dorsal to the spinal cord are destroyed by invading mesodermal connective tissue. Occasionally, islands of ependymal cells or aberrant canals lined with ependyma are seen in the connective tissue dorsal to the spinal cord, as in my first case (fig. 1 *B*, *e.c.*). A common complication of the araphic state is the invagination of mesodermal and cutaneous elements into the spinal

8. Walker, A. E., and Bucy, P. C.: Congenital Dermal Sinuses: A Source of Spinal Meningeal Infection and Subdural Abscesses, Brain **57**:401, 1934.

cord substance, a process which at times may separate the spinal cord into two portions, forming one type of pseudoduplication. At other times hyperplastic or neoplastic growths may develop. It is interesting to note in passing that the teratoid tumors of the spinal cord contain only ectodermal and mesodermal derivatives, with no evidences of endodermal tissues.[9] The ependymal tissue, too, may undergo hyperplasia

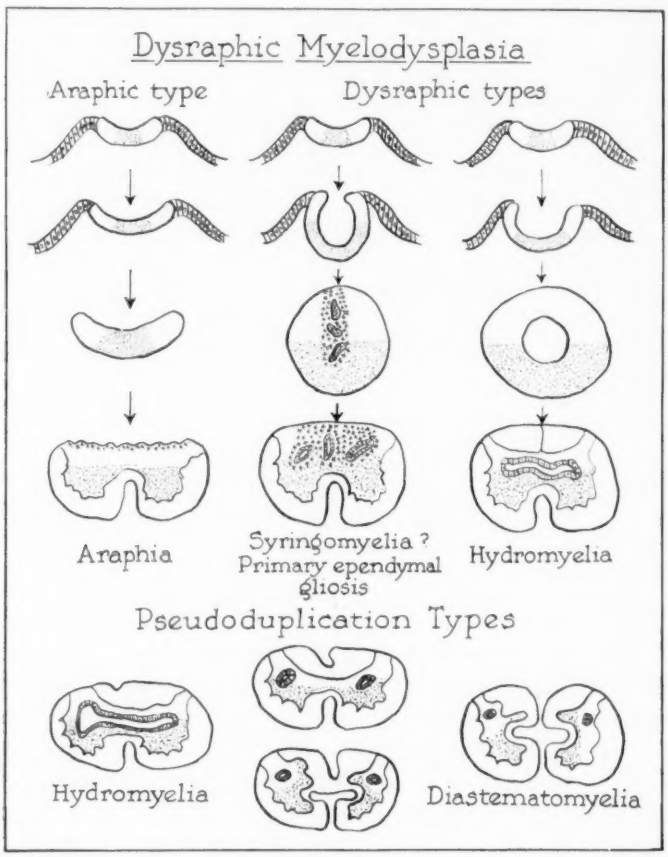

Fig. 8.—Diagrammatic illustration of the development of some of the common forms of dysraphic myelodysplasia.

and result in tumor formation. An interesting example is the case of Mackay,[10] in which an ependymoblastoma in the fourth ventricle had

9. Hosoi, K.: Intradural Teratoid Tumors of the Spinal Cord: Report of Case, Arch. Path. **11**:875 (June) 1931. Bucy, P. C., and Buchanan, D. N.: Teratoma of the Spinal Cord, Surg., Gynec. & Obst. **60**:1137, 1935.

10. Mackay, R. P.: Ependymoblastoma in the Fourth Ventricle with New Bone Formation, Arch. Neurol. & Psychiat. **34**:844 (Oct.) 1935.

islands of new bone formation. In explanation of his case, Mackay stated that the bone arose from mesoblastic cell rests which descended into the portion of the medullary tube that was to form the rhombencephalon. The pathogenesis of the tumor seemed to be characterized by dysraphia, mesoblastic cell inclusion, ependymal proliferation and the formation of new bone.

Dysraphia: Another type of myelodysplasia probably due to defective closure of the neural tube is a form of hydromyelia (fig. 8). This type of hydromyelia may be sharply localized to a few spinal segments. Utchida,[11] in studying the spinal cords of 78 children who had died of various diseases, found 8 instances of such symptomless hydromyelia. At other times the hydromyelia may be extensive and may be associated with pseudoduplication of the spinal cord, a condition which will be discussed later in this paper. Defective closure of the neural tube may also lead to abnormal central canal formation and ependymal proliferation. The development of these anomalies is schematically represented in figure 8. The variations in this type of dysplasia are enormous, ranging from complete absence of the central canal to the presence only of nests of ependymal glia or of several atypical tubules lined with ependyma and surrounded by areas of ependymal cells (figs. 2 and 4), as in my second case. Minor variations of this disorder are common and are clinically silent; every one is familiar with the ependymal nests in the lumbar segments of the spinal cord which replace a central canal. At times the ependymal tissue may extend to the pia posteriorly and occupy the region of the spinal cord usually taken by the fibers of the posterior columns (fig. 2). This ependymal tissue may be hyperplastic, as in my second case, and invade and separate the various ganglionic cell groups in the gray substance. It is common for malformed tissue to be the site of vascular disturbances, and the highly vascularized glial tissue in my case was the site of recent and old extravasations of blood. The ependymal hyperplasia, as well as the hemorrhages, had destroyed many of the ganglion cells and nerve fibers, as evidenced by the degenerated spinal nerve roots (fig. 3 *B*). Such ependymal proliferations may be clinically silent. Zappert,[12] investigating many hundreds of spinal cords of young persons, found many examples of glial increase and hydromyelia. It is important to note that this variety of myelodysplasia may not be associated with a vertebral defect, and thus a clinical diagnosis may be difficult. The clinical symptoms in such cases will be considered later. The ependymal glial proliferation touches on that controversial subject: the pathogenesis of syringomyelia. Suffice it to

11. Utchida, S.: Ueber symptomlose Hydromyelie im Kindesalter, Beitr. z. path. Anat. u. z. allg. Path. **31**:559, 1902.

12. Zappert, cited by Riley.[19]

say that some [13] have asserted that syringomyelia is a developmental anomaly dependent on improper fusion of the neural tube, and others that it is a glial abiotrophy.[14] As the glia in many cases is composed of nests of ependymal cells (fig. 3 *A*), Mackay and Favill [13a] used the term primary ependymal gliosis for hyperplasia of such tissue instead of the term primary central gliosis, which has long been applied to it.

In addition to the changes in the spinal cord in my second case indicative of defective closure of the medullary tube, failure in the migration of neural crest derivatives was evidenced by the presence of spinal ganglia next to the pia mater. Such ectopic ganglia have been recorded by Henneberg and Westenhöfer [15b] and others.

Of particular interest in this study was the so-called duplication in case 3. In following sections of the spinal cord caudally from the cervical region one could see progressively increasing hydromyelia. At the site of the vertebral defect the central canal bifurcated and the substance of the spinal cord began to separate into halves. The separation was completed by a downgrowth of connective tissue in the dorsal

13. (*a*) Mackay, R. P., and Favill, J.: Syringomyelia and Intramedullary Tumor of the Spinal Cord, Arch. Neurol. & Psychiat. **33**:1255 (June) 1935. (*b*) Gerlach, W.: Ein Fall von congenitaler Syringomyelie mit intramedullärer Teratombildung, Deutsche Ztschr. f. Nervenh. **5**:275, 1894. (*c*) Bielschowsky, M., and Unger, E.: Syringomyelie mit Teratom und extramedullärer Blastombildung, J. f. Psychol. u. Neurol. **25**:173, 1920. (*d*) Henneberg, R., and Koch, M.: Zur Pathogenese der Syringomyelie und über Hämatomyelie bei Syringomyelie, Monatschr. f. Psychiat. u. Neurol. **54**:117, 1923.

14. Hassin, G. B.: A Contribution to the Histopathology and Histogenesis of Syringomyelia, Arch. Neurol. & Psychiat. **3**:130 (Feb.) 1920. Petrén, K.: Beiträge zur pathologischen Anatomie und zur Pathogenese der Syringomyelie und der Syringobulbie, Virchows Arch. f. path. Anat. **196**:377, 1909.

15. (*a*) Brouwer, B.: Ueber partielle Anencephalie mit Diastematomyelie ohne Spina bifida, J. f. Psychol. u. Neurol. **20**:173, 1913. (*b*) Henneberg, R., and Westenhöfer, M.: Ueber asymmetrische Diastematomyelie von Typus der "Vorderhornabschnürung" bei Spina bifida, Monatschr. f. Psychiat. u. Neurol. **33**:205, 1913. (*c*) Weil, A., and Matthews, W. B: Duplication of the Spinal Cord with Spina Bifida and Syringomyelia, Arch. Path. **20**:882 (Dec.) 1935. (*d*) Schenk, V. W. D.: Ein Fall von Acranie, Rachischise, Duplicitas medullae usw., Ztschr. f. d. ges. Neurol. u. Psychiat. **146**:369, 1933. (*e*) Kino, F.: Zur Lehre von der Verdoppelung des Rückenmarkes, ibid. **65**:272, 1921. (*f*) Weiting, J.: Zur Anatomie und Pathologie der Spina bifida und Zweiteilung des Rückenmarks, Beitr. z. klin. Chir. **25**:40, 1899. (*g*) Sulzer, P.: Ein Fall von Spina bifida verbunden mit Zweitheilung und Verdoppelung des Rückenmarks, Beitr. z. path. Anat. u. z. allg. Path. **12**:566, 1893. (*h*) Theodor, F.: Ein Fall von Spina bifida mit Doppeltheilung des Rückenmarks (Diastematomyelie), Arch. f. Kinderh. **24**:344, 1898. (*i*) Henneberg, R.: Rückenmarksbefunde bei Spina bifida, Diastematomyelie, kongenitale Syringomyelie, Monatschr. f. Psychiat. u. Neurol. **47**:1, 1920.

portion of the spinal cord directed toward the site of termination of the anterior fissure. This division was then followed by the penetration of branches of the anterior spinal artery into the substance of each half of the cord, which gave rise to secondary anterior fissures. Each spinal cord was enveloped by its own pia, and both were surrounded by a common dura. The development of this form of so-called duplication is diagrammatically represented in figure 8. A consideration of the probable method of development of this type of duplication is necessary for the proper understanding of the internal architecture of such so-called duplications of the spinal cord. A study of the literature shows that all the duplications of this type have the same characteristics.[15] The development of secondary anterior fissures at right angles to the primordial anterior fissure gives the resultant spinal cords the appearance of having been rotated medially through an angle of 90 degrees. As it is not a true duplication but a diastasis of one spinal cord into two parts, the term diastematomyelia is preferred to diplomyelia or duplication. Though diastematomyleia is an example of the dysraphic state to an extreme degree, in Brouwer's [15a] case it was not associated with a bone defect. As each spinal cord in the so-called duplication is derived from one half of the medullary tube, the internal structure is easy to understand. If the separation occurs in the midline each spinal cord has one anterior and one posterior horn. The anterior horn of each may be irregularly divided by the development of a secondary anterior fissure.

With this in mind one can understand the detailed description of the duplication in the case of Weil and Matthews.[15c] They stated:

> In each cord the two anterior horns were separated, but the posterior horns had been united into one . . . (and) only one anterior horn . . . was well developed.
>
> Though there were two anterior horns in each half, only the more anteriorly situated . . . gave rise to an anterior root. . . . In most sections the two (posterior) horns were combined, and only one posterior root arose from it.

From a study of the diagrams in figure 8, it is apparent that the posterior horns had not united into one, but that each posterior horn arose from a single anlage. The single posterior nerve root which arose from the posterior horn was normal. Instead of only one anterior horn being well developed in each section, it is more probable that a single anterior horn had been divided into irregular portions by the development of the anterior fissure.

Ikeda [16] and others suggested that in early embryonic life the caudal part of the spinal cord develops not from an open tube but from a solid

16. Ikeda, M.: Beiträge zur normalen und abnormalen Entwicklungsgeschichte des caudalen Abschnittes des Rückenmarks bei menschlichen Embryonen, Ztschr. f. Anat. u. Entwcklngsgesch. **92**:380, 1930.

bundle of cells in which two or more cavities are formed. Later these tubules become confluent, and the united cavities form the central canal. As the anomalies already described arise in parts other than the caudal segments of the neural tube as well, such an explanation need not be invoked in the case of diastematomyelia.

The differentiation of the varieties of myelodysplasia—dysraphic and others—from artefacts of the spinal cord secondary to faulty removal and to similar causes has been excellently demonstrated by Van Gieson.[17]

CLINICAL PHENOMENA

The clinical features of spina bifida occulta and myelodysplasia have been adequately reviewed in the excellent works of Brickner [18] and Riley.[19] Since spina bifida most often affects the lumbosacral regions, the clinical signs and symptoms are as a rule, in the lower extremities. Thus, Oppenheim [20] reported cases of congenital shortening, atrophy and paresis of one leg, with partial sensory disturbances. Instances of familial gangrene of the feet and perforating ulcers have been reviewed by Wexberg.[21] According to Bremer [7] and others, the dysraphic state represents a definite hereditary constitutional type. Fuchs [22] described a clinical syndrome which he properly designated myelodysplasia. It consisted of weakness of the sphincters, usually manifested by enuresis; sensory, trophic and vasomotor disturbances in the feet, of syringomyelic type; cleft arch of one or more vertebrae and cutaneous changes, such as hypertrichosis and fovea coccygea. As myelodysplasia (the pathologic entity) may occur anywhere in the spinal cord, the symptoms vary with its locality. Since the primary ependymal glia may undergo hyperplasia, break down and become invaded by mesodermal connective tissue, or may be the site of repeated hemorrhages, as in my second case, it is not uncommon for such a congenital disorder to be silent until puberty, or even later. Trauma to the poorly innervated extremity often brings to light the initial signs of such a neurologic disorder, as in the case of de Vries [23] in which clubfoot developed at the age of 30 years, after

17. Van Gieson, I.: A Study of the Artefacts of the Nervous System, New York M. J. **56**:337-365 and 421, 1892.

18. Brickner, W.: Spina Bifida Occulta, Am. J. M. Sc. **155**:473, 1918.

19. Riley, H. A.: Syringomyelia or Myelodysplasia, J. Nerv. & Ment. Dis. **72**:1, 1930.

20. Oppenheim, H., cited by Riley.[19]

21. Wexberg, E.: Zur Frage der konstitutionellen Disposition zur Syringomyelie, Ztschr. f. d. ges. Neurol. u. Psychiat. **79**:114, 1922.

22. Fuchs, A.: Ueber den klinischen Nachweis kongenitaler Defektbildungen in den unteren Rückenmarksabschnitten (Myelodysplasie), Wien. med. Wchnschr. **59**:2142 and 2262, 1909.

23. de Vries, E.: Spina Bifida Occulta and Myelodysplasia with Unilateral Clubfoot Beginning in Adult Life, Am. J. M. Sc. **175**:365, 1928.

an injury resulting in trophic disturbances. It is important to remember that the spinal cord may be affected without a bone defect, as shown in my second case and in those of Woltman [24] and Brouwer.[15a]

Symptoms of involvement of the spinal cord may arise also from concomitant or associated pathologic conditions, such as tumors, bands of connective tissue and adhesions between the skin and the spinal membranes pressing on the underlying cord. When the spinal cord is affected in the cervical (Hassin [25]) or dorsal (Reiner [26]) portion, spastic paralysis in the lower extremities may occur.

Since the term spina bifida cystica signifies an overt vertebral defect accompanied by a mass, and spina bifida occulta a latent vertebral defect, I believe that the term "spinal dysraphism" or "the spinal dysraphic state" more fully designates the disorders belonging to the so-called spina bifida group. The disorders may involve cutaneous, mesodermal or neural elements, singly or in combination.

SUMMARY

1. To the spinal dysraphic state belong a pleomorphic group of pathologic disorders which may be cutaneous, mesodermal or neural in origin.

2. Cutaneous spinal dysraphism may consist of cutaneous defects, hypertrichosis, pilonidal cysts and congenital dermal sinuses.

3. Mesodermal spinal dysraphism consists of defects in fusion of the vertebral neural arch and of the dura mater.

4. Neural spinal dysraphism consists of the dysraphic forms of myelodysplasia, the hyperplastic and neoplastic growths associated with myelodysplasia, and some forms of hydromyelia, primary ependymal gliosis and pseudoduplication of the spinal cord, as well as ectopic spinal ganglia.

5. The neural forms of dysraphia may be present without cutaneous or mesodermal defects.

6. The clinical symptoms of spinal dysraphism are variable, depending on the location and extent of the developmental defect, as well as on the development of secondary changes.

7. Defect in the vertebral neural canal and dural dysraphia are, I believe, the sine qua non of meningocele formation.

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24. Woltman, H. W.: Spina Bifida: A Review of One Hundred and Eighty-Seven Cases, Including Three Associated Cases of Myelodysplasia Without Demonstrable Bony Defect, Minnesota Med. **4**:244, 1921.

25. Hassin, G. B.: Spina Bifida Occulta Cervicalis, Arch. Neurol. & Psychiat. **14**:813 (Dec.) 1925.

26. Reiner, M.: Ueber einen Fall von Spina bifida occulta dorsalis, Wien. klin. Rundschau **15**:325, 1901.

DISCUSSION

DR. R. P. MACKAY: Although Dr. Lichtenstein has carefully avoided the question of syringomyelia in this excellent presentation, I believe he has made an important contribution to its solution. One can scarcely doubt the presence of syringomyelia in his second and his third case, as indicated by primary ependymal gliosis associated with the abnormal central canals. I cannot find good evidence for the view that syringomyelia results from a biologically defective glia; it is confusing to regard it as "merely" cavitation in an intramedullary astrocytoma. Although cavitation of the cord may arise from numerous other causes, such as softening, hemorrhage or trauma, a careful study of such cases as those discussed by Dr. Lichtenstein seems to indicate that genuine syringomyelia arises from a process of dysraphia. It would thus appear to be the result of a disturbance in the final step in the formation of the median raphe of the neural tube, with disorientation of the ependymal spongioblasts and their proliferation to form "primary ependymal gliosis." In the cases reported by Dr. Lichtenstein this has occurred, but in addition much more marked dysraphia has involved both mesodermal and ectodermal structures. The slides suggest an ependymoblastoma in the second case. If this is a correct interpretation, there is provided a new illustration of the intimate relation between developmental anomalies and neoplasia in the nervous system.

Dr. Lichtenstein said that there was no clinical evidence of syringomyelia in any of these cases. May I ask how exhaustive was the evidence on that point in the hospital records at his disposal? Neurologic abnormalities must have been present in view of the extreme pathologic changes in the spinal cords. Why was poliomyelitis suspected?

DR. BEN W. LICHTENSTEIN: In the clinical histories of the cases presented there was no evidence of spina bifida in other members of the family. In many cases, however, the family history was incomplete. In answer to Dr. Mackay: In the first and third cases the patients were infants with spina bifida sacs in the lumbosacral region, while the second boy aged 4 came into the hospital acutely ill and no detailed neurologic examination was performed. As to the presence of syringomyelia, I may say that the ependymal tissue in the second case was hyperplastic rather than neoplastic. Both the hyperplastic ependymal glia and the neoplastic ependymal growths, ependymomas, are often associated with cavity formation.

ADVANTAGES AND DANGER OF COMBINED ANOXIC AND INSULIN SHOCK

REPORT OF ANIMAL EXPERIMENTS WITH A POSSIBLE METHOD OF TREATMENT FOR SCHIZOPHRENIA

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The effect of short periods of simple anoxia uncomplicated by the accumulation of carbon dioxide or by anesthetics has been studied in experiments on progressive thrombosis since the beginning of 1937. The experimental procedure employed was briefly denoted as anoxic shock. Steadily flowing oxygen-nitrogen mixtures in which the oxygen was gradually reduced produced a slowly but progressively increasing anoxia, which caused, within fifteen to thirty minutes, a state of gasping respiration or the arrest of respiration. The symptoms elicited were so much like those described by observers of Sakel's [1] insulin shock that in his detailed report on insulin shock, given at the staff meeting of the Memorial Hospital, Albany, N. Y., on Nov. 23, 1937, Dr. W. B. Cornell seemed to describe all the symptoms I had observed in rabbits during anoxic shock. I was so impressed that in the discussion which followed I dared to say that I considered it more than justified to make a test of the therapeutic effect of anoxic shock on schizophrenic patients. This suggestion was based, aside from the experimental observations mentioned, on the then known facts of the mechanism of insulin shock. Himwich and Nahum [2] had shown that metabolism of the brain depends almost exclusively on carbohydrates supplied by the blood. Hypoglycemia occurring during insulin shock, therefore, would produce starvation of the brain cells. The reduced utilization of oxygen by the brain during insulin shock (Dameshek, Meyerson and Stephenson [3] and Himwich

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1. Sakel, M.: Schizophreniebehandlung mittels Insulin-Hypoglykämie sowie hypoglykämischen Schocks, Wien. med. Wchnschr. **84**:1211, 1934.

2. Himwich, H. E., and Nahum, L. H.: The Respiratory Quotient of the Brain, Am. J. Physiol. **101**:446, 1932.

3. Dameshek, W. A.; Meyerson, A., and Stephenson, C.: Insulin Hypoglycemia: Mechanism of the Neurologic Symptoms, Arch. Neurol. & Psychiat. **33**:1 (Jan.) 1935.

and Fazekas [4]) was concluded to be a logical sequence of want of material to be oxidized. It was inferred that the converse also ought to be true, namely, that want of oxygen would make it impossible for the cells of the brain to utilize the carbohydrates supplied by the blood, for the oxygen requirements of the brain are high as compared with those of other organs. Chang [5] has recently shown that even the isolated heart cannot maintain its activity for more than a few minutes by anaerobic breakdown of carbohydrates. Thus, it was expected that deficiency of oxygen would affect the same site and mechanism in the brain as want of carbohydrates. This conjecture gave a logical explanation for the close resemblance observed between the symptoms elicited by anoxic and those by insulin shock. Since animal experiments had shown that, with the proper precautions, anoxic shock was not a dangerous procedure, it was expected that the favorable therapeutic effect of insulin shock on schizophrenic patients could also be produced by anoxic shock, and perhaps with considerably less danger. Comparative anatomic studies on insulin and anoxic shock, subsequently started, showed indeed that the changes in the brain produced by the two types of shock are in principle identical.[6] These observations gave a broader basis for the therapeutic suggestion previously made.

A striking similarity between the leading symptoms elicited by insulin shock and those by oxygen deficiency had previously been noted by several authors. Olmsted and Logan,[7] in 1923, were the first to describe this similarity. They observed that the blood became dark during insulin convulsions and assumed, therefore, that the convulsions were due to anoxia, possibly produced by a depressant effect of insulin on the respiratory center. Kleitman and Magnus [8] confirmed the similarity of insulin convulsions to anoxic convulsions but did not accept the theory advanced, since they were able to produce insulin convulsions despite arterialization of the blood by continuous artificial respiration. Nevertheless, after the studies of Holmes,[9] Dickens and Greville,[10]

4. Himwich, H. E., and Fazekas, J. F.: The Effect of Hypoglycemia on the Metabolism of the Brain, Am. J. Physiol. **119**:335, 1937.

5. Chang, I.: Asphyxial Arrest of the Isolated Rabbit's Auricle, Quart. J. Exper. Physiol. **27**:113, 1937.

6. Tannenberg, J.: Comparative Studies on Symptomatology and Anatomical Changes Produced by Insulin Shock and Anoxic Shock, Am. J. Path. **14**:688, 1938; Proc. Soc. Exper. Biol. & Med. **40**:94, 1939.

7. Olmsted, J. M. D., and Logan, H. D.: The Effect of Insulin on the Central Nervous System and Its Relation to the Pituitary Body, Am. J. Physiol. **66**:437, 1923.

8. Kleitman, N., and Magnus, R.: Zur Wirkung des Insulins auf das Centralnervensystem, Arch. f. d. ges. Physiol. **205**:148, 1924.

9. Holmes, E. G.: Oxidations in Central and Peripheral Nervous Tissue, Biochem. J. **24**:914, 1930.

10. Dickens, F., and Greville, G. D.: Metabolism of Normal and Tumor Tissue: VIII. Respiration in Fructose and in Sugar Free Media, Biochem. J. **27**:832, 1933.

Wortis,[11] Dameshek, Myerson and Stephenson,[3] Himwich and Fazekas [4] and Glickman and Gellhorn,[12] it was more and more accepted that anoxia of the brain had some definite part in the pathogenesis of insulin convulsions. Holmes observed that an increasing uptake of oxygen by brain tissue in Warburg's apparatus paralleled an increasing concentration of dextrose and that the uptake was definitely reduced when the animals had been given injections of insulin shortly prior to the experiment. Dickens and Greville observed a large decrease in the respiration of brain tissue with the deprivation of dextrose. Wortis confirmed the observation of Holmes, Dameshek and Himwich and their associates, made in human and animal experiments, that the oxygen uptake by the brain was materially reduced during insulin shock. According to Glickman and Gellhorn, moderate anoxemia precipitated and aggravated insulin convulsions in the rat. All these authors interpreted their observations on the assumption that insulin hypoglycemia somehow depressed the uptake and utilization of oxygen by the brain and that the anoxic state produced thereby in the brain was directly to blame for the severe symptoms at the peak of an insulin shock. Palisa [13] stressed the great similarity of symptoms observed during prolonged insulin shock and those described after resuscitation from various kinds of suffocation, such as hanging, burial by avalanche and poisoning by carbon monoxide. Investigators using anatomic methods, such as Stief and Tokay [14] and Weil, Liebert and Heilbrunn,[15] also stated the belief that the generalized disease of the neurons which they had observed in cases of insulin shock was the result of lack of oxygen or of intracellular anoxia.

Thus, I concluded that anoxia applied directly in one form or the other might achieve the same therapeutic results as insulin shock in patients with schizophrenia. Himwich, Alexander and Lipetz,[16] and

11. Wortis, S. B.: Respiratory Metabolism of Excised Brain Tissue: Effects of Some Drugs on Brain Oxidations, Arch. Neurol. & Psychiat. **33**:1022 (May) 1935.

12. Glickman, N., and Gellhorn, E.: The Effect of Oxygen Deficiency on the Sensitivity of Rats to Insulin, Am. J. Physiol. **121**:358, 1938.

13. Palisa, C.: Zur Frage der hirnpathologischen Erscheinungen des Insulinshocks, Arch. f. Psychiat. **108**:633, 1938.

14. Stief, A., and Tokay, L.: Beiträge zur Hirnpathologie der experimentellen Insulinvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **139**:434, 1932; **153**:561, 1935.

15. Weil, A.; Liebert, E., and Heilbrunn, G.: Histopathologic Changes in the Brain in Experimental Hyperinsulinism, Arch. Neurol. & Psychiat. **39**:467 (March) 1938.

16. Himwich, H. E.; Alexander, F. A. D., and Lipetz, B.: Effect of Acute Anoxia Produced by Breathing Nitrogen, on the Course of Schizophrenia, Proc. Soc. Exper. Biol. & Med. **39**:367, 1938.

Gellhorn,[17] independently following up previous work, recently came almost simultaneously to the same conclusion. In the spring of 1938, when I exhibited the results of my comparative anatomic studies of insulin and anoxic shock at a meeting of the American Association of Pathologists and Bacteriologists at Atlantic City, N. J., Gellhorn read a paper at Chicago in which he advocated anoxia as a rational therapy for schizophrenia. Himwich, Alexander and Lipetz, a few months later, were already able to give a favorable report of tests with anoxia conducted on schizophrenic patients. At the meeting of the American Psychiatric Association in 1939, Strecker, Flaherty, Rome and Zintl [18] reported briefly on the nitrogen treatment of schizophrenia, almost coincidentally with the publication of a paper by Fraser and Reitmann,[19] in England.

The idea of anoxia as a treatment of schizophrenia is old and can be traced back to Wagner von Jauregg (1889).[20] He observed transitory and lasting improvement, respectively, in the psychotic conditions of 2 patients who had been resuscitated after hanging themselves. He also referred to 2 similar cases observed by other authors; on the whole, however, he was cautious in evaluation of the therapeutic effect of anoxia, comparing it with the similar, but also uncertain, effect of febrile diseases on psychoses. Strauss [21] discussed the possible therapeutic effect of anoxia on manic-depressive psychoses. Loevenhart, Lorenz and Water [22] reported transitory periods of improvement in schizophrenic patients treated with sodium cyanide or carbon dioxide in high concentrations. Their results, which were confirmed by Leake, Wood, Botsford and Guedel,[23] in reality must be considered an effect of the

17. Gellhorn, E.: Effects of Hypoglycemia and Anoxia on the Central Nervous System: A Basis for a Rational Therapy of Schizophrenia, Arch. Neurol. & Psychiat. **40**:125 (July) 1938.

18. Strecker, E. A.; Flaherty, J. A.; Rome, H., and Zintl, W.: Electrocardiographic Observations in Convulsive and Nitrogen Therapy, read before the ninety-fifth annual meeting of the American Psychiatric Association, Chicago, May 8-12, 1939.

19. Fraser, R., and Reitmann, F.: A Clinical Study of Effects of Short Periods of Severe Anoxia, with Special Reference to Mechanism of Action of Cardiazol Shock, J. Neurol. & Psychiat. **2**:125, 1939.

20. Wagner von Jauregg, J.: Ueber einige Erscheinungen im Bereiche des Centralnervensystems, welche nach Wiederbelebung Erhängter beobachtet werden, Jahrb. f. Psychiat. u. Neurol. **8**:313, 1889.

21. Strauss, H.: Strangulationsfolgen und Hirnstamm, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:363, 1931.

22. Loevenhart, A. S.; Lorenz, W. F., and Water, R. M.: Cerebral Stimulation, J. A. M. A. **92**:880 (March 16) 1929.

23. Leake, C. D.; Wood, D. A.; Botsford, M. E., and Guedel, A. E.: The Effects of the Administration of Carbon Dioxide and Oxygen in Catatonic Dementia Praecox, Anesth. & Analg. **9**:62, 1930.

ensuing anoxia. D'Elseaux and Solomon,[24] in specific studies, observed that the degree of acidosis, the high carbon dioxide content of the blood, the loss of consciousness or the increase in ventilation was not the real cause of the therapeutic effect which they noted.

In the report to be given only results of animal experiments will be presented. Anoxic shock was intentionally extended to the utmost limit endurable. Special consideration was given to signs indicating the approach of danger.

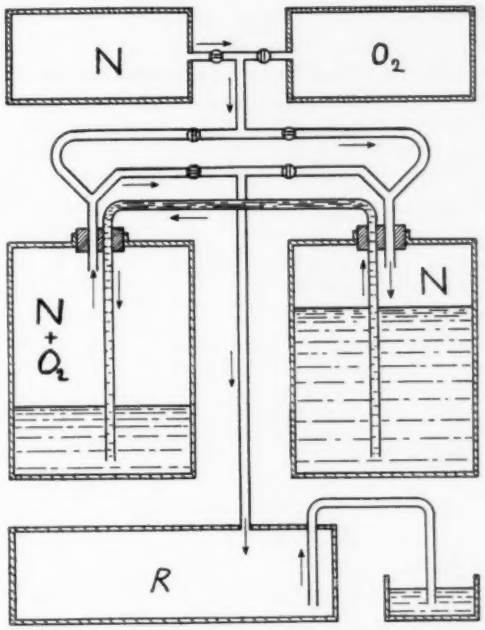

Fig. 1.—Apparatus employed for anoxic shock in rabbits, *N* indicating nitrogen, O_2 oxygen and *R* the rabbits' chamber.

METHOD

In a single experiment 4 to 6 rabbits were kept together in a large glass container through which a mixture of oxygen and nitrogen was steadily flowing. Figure 1 shows the simple apparatus employed. The percentage of oxygen was so slowly diminished that the rabbits approached the end stage of the experiment, the onset of gasping respiration, without having shown any excitement or restlessness. This was made the decisive factor in determining the rapidity of the diminution of oxygen. Analysis of samples of the gas mixtures employed showed about 6 per cent oxygen at the peak of the shock. Close observation of the animals, however, was the best indicator of the stage of the shock, the approach

24. D'Elseaux, F. C., and Solomon, H. C.: Use of Carbon Dioxide Mixtures in Stupor Occurring in Psychoses, Arch. Neurol. & Psychiat. **29**:213 (Feb.) 1933.

of the critical phase of the experiment and any accumulation of carbon dioxide. The duration of a single shock varied from fifteen to thirty minutes. Forced respiration with the aid of auxiliary respiratory muscles, a characteristic sign of accumulation of carbon dioxide, was not observed in these experiments. During preliminary experiments, carbon dioxide was eliminated by absorption with potassium hydroxide. Later, the steady flow of the gas mixture was found to be sufficient for its elimination. The resistance of individual rabbits to anoxia varied little when 4 to 6 animals were treated simultaneously, provided generally healthy rabbits that had been similarly treated previously were used together in such a series. With the arrangement described, more than three hundred and fifty anoxic shocks were administered to 38 rabbits. The number of shocks per animal varied from one to fifty-one. The total period of an experiment for a single animal lasted from one to sixty days. The periods of rest between shocks varied from fifteen minutes to more than a week. A few animals were subjected to ten or fifteen anoxic shocks on a single day.

The effect of combined anoxia and insulin shock was studied in 14 additional rabbits, 8 of which were treated daily with doses of insulin of about 1 unit per kilogram of body weight for seven weeks. They were not made to fast prior to the injections of insulin, so that the dose remained below the threshold of that producing convulsions. The anoxic shocks were administered four times to each animal, two and five hours after the injections of insulin, at a time when the insulin hypoglycemia was spontaneously disappearing. Six rabbits treated with shock doses of 2 units per kilogram of body weight or more were subjected to anoxic shock one or several hours after the injection of insulin for the study of the simultaneous effect of insulin and anoxia on the blood sugar content. As controls, about 50 additional rabbits that had previously been used for various other purposes in the laboratory were subjected to, and finally killed by, the sudden and total deprivation of oxygen in an atmosphere of nitrogen.

RESULTS

The deliberately slow reduction of oxygen as employed in these experiments made the oncoming anoxia imperceptible, and thereby prevented active resistance of the rabbits and violent reflex actions which occur in suddenly enforced anoxia. Haldane [25] and Izquierdo [26] also emphasized this difference in the results of slow and of abrupt reduction of oxygen. The main symptoms during anoxic shock were: moderate increase in the respiratory rate; slowly increasing tiredness and listlessness; muscular weakness that became progressively more evident; changes in the posture, such as elevation and backward throwing of the head; marked hypersalivation and, finally, increasing inability to remain in a sitting position and gradual lapse into a semicomatose state. The mucous membranes gradually became cyanotic, as did finally the blood in the dilated artery of the ear. At this stage the respiratory rate began to decrease, and soon breathing became definitely slower and shallower than it had been at the beginning of the experiment. Within the next few minutes deep gasps were observed, which interrupted the regular respiratory rhythm. Respiration ceased one or two minutes after the appearance of the first gasping inhalation. The heart was still beating at this time, unless

25. Haldane, J. S.: A Lecture on the Symptoms, Causes and Prevention of Anoxemia, Brit. M. J. **2**:65, 1919.

26. Izquierdo, J. J.: The Polycythemia of Acute Anoxemia and Its Relation to the Sympathico-Adrenal System, Am. J. Physiol. **86**:145, 1928.

anoxic shock was complicated by preexisting cardiac disease, frequent repetitions of the shock with insufficient intervals of rest or simultaneous administration of various drugs.

Resaturation of the blood with oxygen after the termination of anoxic shock was accomplished within a few seconds, as was indicated by the swift change in color of the mucous membranes. Even after the arrest of respiration, artificial respiration usually was required for only a few moments. Immediately after the resaturation of the blood with oxygen, more or less widespread muscular twitchings, up to violent general seizures, were observed, which turned the rabbit over from side to side for one-half minute or longer. Coincident with the seizures the rabbit lapsed into deep coma, with maximal dilatation of the pupils and loss of all reflexes, even if it had previously been merely in a semicomatose state. It was characteristic that the seizures began just after resaturation of the blood with oxygen, about ten to fifteen seconds after interruption of the anoxia. The duration and severity of the attacks were not predictable in an individual animal, for the seizures were not dependent simply on the depth and duration of the preceding anoxic shock.

Such seizures have also been observed in human beings. Wagner von Jauregg [20] observed them in persons resuscitated after attempted suicide by hanging. They began characteristically when the respiration again became regular. Gerstmann [27] saw them in persons resuscitated after suffocation by snow avalanches, and Strauss [21] analyzed them as signs of reawakening of the nucleus ruber.

After the seizures the rabbits generally recovered quickly and were in the normal sitting position within five to ten minutes.

By the cautious addition and reduction of oxygen, a state of marked anoxia, close to that producing gasping respiration, could be maintained for about ten to twenty minutes without arousing the animal and without having it lapse into coma. Such a prolongation of definite anoxia was not especially dangerous. After its termination reactions similar to those described after the interruption of the anoxic shock at its peak were observed, though usually in a milder form. Avoidance of the greater risk at the peak of the shock seemed worth the greater attention required, namely, readiness for interruption at the first sign of oncoming paralysis of the respiratory center, such as definite slowing of the respiratory rate.

For comparison, a short description is given of the course of sudden total deprivation of oxygen produced by exposing rabbits to an atmosphere of pure nitrogen. These rabbits quickly grew restless and struggled for escape; the respiratory rate increased rapidly; the head was thrown backward; the animal finally fell on its side, and a few seconds later, almost coincident with arrest of the respiration, violent seizures usually occurred. By immediate removal from the nitrogen chamber and artificial respiration most of these rabbits could also be resuscitated. However, even brief delays resulted in paralysis of the vasomotor center and death. The lungs of these rabbits were filled with nitrogen, and their blood was already at a dangerously low level of oxygen at the moment convulsions began. In contrast, at the onset of convulsions the lungs of the rabbits subjected to slowly progressing anoxia were filled with oxygen and their blood was saturated with oxygen. It was therefore definitely more risky to continue sudden and complete deprivation of oxygen to this degree. Termination prior to the stage of

27. Gerstmann, J.: Ueber einige Störungen im Bereich des Zentralnervensystems in Fällen von Lawinenverschüttung nach deren Wiederbelebung, Monatschr. f. Psychiat. u. Neurol. **43**:271, 1918.

convulsion, however, made the period of anoxia for the tissues so brief that a definitely lasting effect on the cells could scarcely be expected. Tests on anoxia in man, at least those conducted by Schneider and Truesdell,[28] Larsen[29] and McFarland,[30] seemed to show this. Only numerous repetitions of such short deprivations of oxygen at short intervals may have a chance of producing lasting changes in the tissue. In my experience, each repetition of anoxic shock added new moments of uncertainty as to the ability of the animal to withstand it, making each shock more hazardous than the preceding one. Armstrong[31] recently reported similar observations in aviators.

SPECIFIC DANGER OF FREQUENT REPETITION OF ANOXIC SHOCK

The first anoxic shock, continued even up to the arrest of respiration, was not particularly dangerous for a normal rabbit. Artificial respiration within a few seconds usually was successful in restoring the animal. One exception observed proved to be only a confirmation of this rule. This rabbit, revived by a short period of artificial respiration, was seized with violent convulsions. However, instead of the usual recovery afterward, respiration ceased anew and the rabbit died in spite of repetition of the artificial respiration. Preexisting, unusually widespread, chronic myocarditis was found to be the cause of this unusual reaction.

With repetition of anoxic shock several times on the same day or on a series of successive days, it became increasingly unsafe to continue anoxia, even for a short period, after the first gasping inhalation. Sudden and fatal hemorrhagic pulmonary edema, with the appearance of bloody foam at the nose and mouth, not infrequently terminated the experiment under such conditions. Standstill of the heart accompanied, or even preceded, the arrest of respiration in these rabbits. Artificial respiration and intracardial injections of epinephrine were without beneficial results. At autopsy the lungs were observed to be maximally distended and filled with edematous fluid. Previously normal animals, which were intentionally killed by a single anoxic shock, showed collapsed lungs at autopsy, but no pulmonary edema. The same rabbits that during the first anoxic shocks had withstood well an oxygen level of 6 or 7 per cent showed signs of exhaustion at a level of 10 and 12 per cent after a series of six or seven repetitions of the shock on successive days. Rabbits which, after several shocks on preceding days, were ten or fifteen times subjected to anoxic shocks on a single day survived this

28. Schneider, E. E., and Truesdell, D.: The Circulation Responses of Man to a Sudden and Extreme Anoxemia, Am. J. Physiol. **65**:379, 1923.

29. Larsen, K.: Effect of Anoxemia on Human Electrocardiogram, Acta med. Scandinav., 1936, supp. 78, p. 141.

30. McFarland, R. M.: The Psychological Effects of Oxygen Deprivation (Anoxemic) on Human Behavior, Arch. Psychol., 1932, no. 145.

31. Armstrong, H. G.: Anoxia in Aviation, J. Aviation Med. **9**:84, 1938.

treatment, but when they were killed later they exhibited large anemic infarctions of the posterior wall of the left ventricle of a size that was even grossly recognizable (compare the two parts of figure 2).

Other rabbits treated with anoxic shocks on six or more successive days showed, when killed, small ruptures of muscular fibers of the skeletal musculature in all stages of healing. In 1 of them the entire

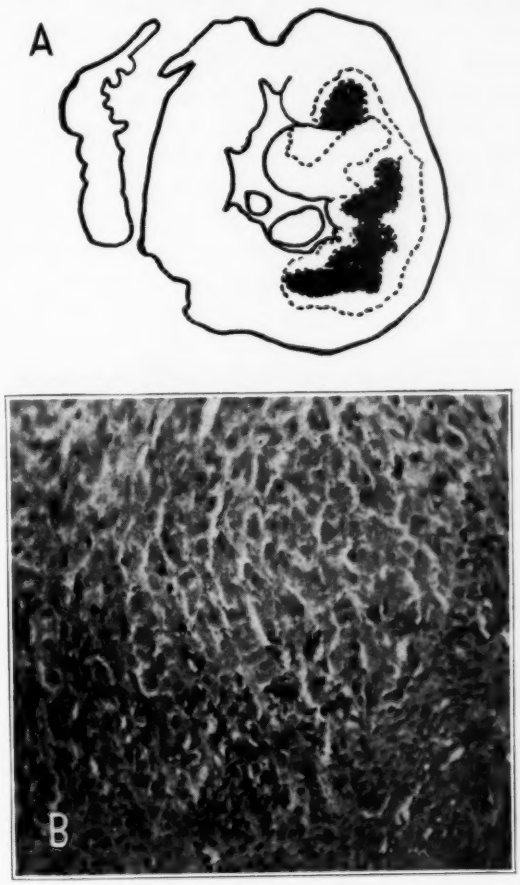

Fig. 2.—*A*, camera lucida drawing of a cross section of the heart of a rabbit. The anemic infarction within the wall of the left ventricle is indicated by blackened areas. The broken lines surrounding them delimit the zone occupied by granulation tissue. *B*, a microscopic enlargement of the borderline of the cardiac infarction. This rabbit was killed eight days after having been subjected to eleven anoxic shocks in one day.

superficial layers of the iliopsoas muscle were ruptured on both sides. Rabbits killed after a few anoxic shocks exhibited peculiar hydropic changes in the muscle fibers and swelling and slight edema in the cardiac

musculature, similar to the lesions described in the hearts of rabbits subjected to prolonged insulin shock (Tannenberg [32]). These changes can be regarded as entirely reversible, if sufficient time is given, but may be the basis of more severe changes, such as were observed by Martin, Loevenhart and Bunting,[33] if a repetition of anoxic shock follows before full recovery is attained.

My experience that repetition of anoxic shock within short intervals is especially dangerous is confirmed by the report of Campbell,[34] who found it impossible to acclimatize animals to an oxygen content of the air of less than 10 per cent, and by the great loss of animals Lehmann [35] experienced when he tried to train mice to endure high altitudes by repeated exposures to carbon monoxide. Studies by Tureen [36] have given a basis for determining the best interval between two successive anoxic shocks. After temporary occlusion of the blood vessels to the spinal cord, he found striking degenerative changes between the seventh and the seventy-second hour. The inflammatory reaction was at its height on the second and third days, and regeneration of Nissl granules began on the third day but was not completed before the seventh day. Functional recovery was attained much earlier than the anatomic regeneration.

COMBINATION OF ANOXIC SHOCK AND INSULIN SHOCK

Both insulin shock and anoxic shock produce their main effects by interfering with cerebral metabolism, by withholding either the indispensable carbohydrates or the oxygen, which is equally indispensable for the utilization of the former. Anoxic shock, as employed in these studies, elicited marked hyperglycemia, especially when followed by seizures. This hyperglycemia was able to overcome, at least temporarily, even marked hypoglycemia produced by insulin in shock doses (compare the representative curves in figures 3 and 4). The administration of insulin and anoxic shocks simultaneously, therefore, did not promise much advantage over that of either alone. The successive administration

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32. Tannenberg, J.: Pathological Changes in the Heart, Skeletal Musculature and Liver in Rabbits Treated with Insulin in Shock Dosage, Am. J. Path. **15**:25, 1939.

33. Martin, H. G.; Loevenhart, A. S., and Bunting, C. H.: The Morphological Changes in the Tissues of the Rabbit as a Result of Reduced Oxidation, J. Exper. Med. **27**:399, 1918.

34. Campbell, J. A.: Note on Some Pathological Changes in the Tissues During Attempted Acclimatisation to Alteration of Oxygen Pressure in the Air, Brit. J. Exper. Path. **8**:347, 1927.

35. Lehmann, G.: Die Wirkung vorhergehender Behandlung mit CO auf die Höhentoleranz von Mäusen, Luftfahrtmed. Abhandl. **2**:137, 1938.

36. Tureen, L. L.: Effect of Experimental Temporary Vascular Occlusion of the Spinal Cord: I. Correlation Between Structural and Functional Changes, Arch. Neurol. & Psychiat. **35**:789 (April) 1936.

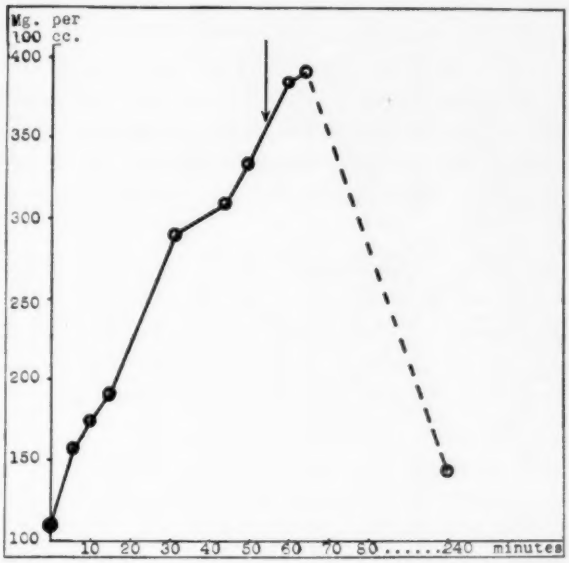

Fig. 3.—A typical blood sugar curve obtained from a rabbit during an anoxic shock. The arrow indicates the moment at which the anoxic shock was interrupted at its peak. It was followed by convulsions, which lasted for about one minute.

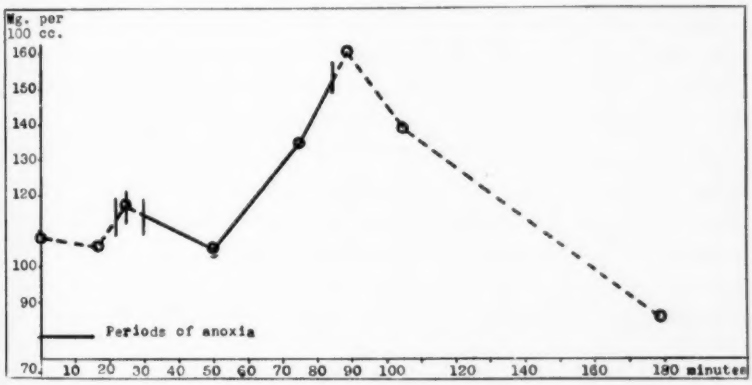

Fig. 4.—A typical curve obtained from a rabbit, showing the simultaneous effect of insulin and anoxia on the blood sugar. After withdrawal of the first blood sample 2.9 units of insulin per kilogram of body weight was injected. The periods of anoxia are indicated by solid lines.

of the two shock treatments, however, seemed to have different results, in accordance with expectations. The effect of anoxic shock produced several hours after an injection of insulin was definitely enhanced. Shock doses of insulin (2 units or more per kilogram of body weight) had the same effect as frequent preceding anoxic shocks without sufficient intervals of rest. The respective animals were rendered so sensitive to anoxia that they died of hemorrhagic pulmonary edema unless anoxic shock was immediately terminated at the appearance of the first gasping inhalation.

Insulin in smaller, subconvulsive doses rendered the rabbits also more sensitive to anoxic shock that was induced two or five hours later. These rabbits, however, did not show such severe and dangerous reactions as those given injections of the large doses of insulin. Their increased sensitivity was indicated by the relatively high oxygen level which brought about the peak of the shock.

There are some interesting reports in the literature about the combined effect of anoxia and substances which elicit convulsions. Archov [37] found that lowered barometric pressure enhanced the convulsive effect of sodium phosphate. Glickman and Gellhorn [12] observed that rats under the same condition were more sensitive to insulin. Moderately lowered atmospheric pressure, however, does not preclude the effect of insulin on the blood sugar. McQuarrie and Ziegler,[38] on the other hand, reported that under anoxic conditions insulin failed to elicit convulsions in dogs, although the same level of hypoglycemia was reached that elicited convulsions under atmospheric pressure. Gellhorn and Packer [39] confirmed this experiment and found further that a short period of anoxia counteracted insulin hypoglycemia, whereas a period of two hours enhanced it, in spite of the presence of glycogen in the liver.

Our experiments were devised from a different point of view. It was assumed, in analogy to the efficacy of Sakel's insulin shock, that in order to have a therapeutic effect anoxic shock must produce definite changes in the brain which would last for some time and probably would also leave traces that were anatomically recognizable. Anoxic shock in man, however, must be a temporarily limited procedure in order to avoid damage to important parenchymatous organs other than the brain; such

37. Archov, N.: On the Pathogenesis of the Convulsive Reaction at Diminished Atmospheric Pressure, Med. zhur. **7**:1027, 1934.

38. McQuarrie, I., and Ziegler, M. R.: Mechanism of Insulin Convulsions: II. Effects of Varying Partial Pressures of Atmospheric Oxygen, Nitrogen and Carbon Dioxide, Proc. Soc. Exper. Biol. & Med. **39**:525, 1938.

39. Gellhorn, E., and Packer, A. C.: Influence of Anoxia on Glycogenolytic Action of Adrenalin, Proc. Soc. Exper. Biol. & Med. **41**:345, 1939.

injuries are well known since the studies of von Schrötter,[40] Rosin [41] and many others and may secondarily endanger life. Brief periods of complete deprivation of oxygen had great disadvantages, as already shown. Therefore, a procedure was sought which, although more slowly effective, would gradually weaken the cells of the brain primarily or even exclusively and thereby increase their sensitivity to a subsequent anoxic shock. It was assumed that even a moderately deep anoxic shock would have a more lasting effect on a brain so prepared than an excessive shock on an unprepared brain. Insulin in moderate doses seemed to be the ideal substance for the purpose. A dose of about 1 unit per kilogram of body weight given to the series of 8 rabbits over seven weeks did not produce shock or severe symptoms. The blood sugar level did not fall below 60 or 50 mg. per hundred cubic centimeters, but this was sufficient to produce some effect of starvation on the brain cells, which was evident by listlessness and tiredness of the animals. The best time to administer anoxic shock was considered to be the moment when the rabbits showed signs of spontaneous recovery from the hypoglycemia. This was between the third and the sixth hour after the injection of insulin. At that time the blood sugar level began to rise again, and the rabbits became spontaneously more alert and began to move about.

The acutely effective anoxic shock produced during this period proved indeed to be more efficacious, and if it has any therapeutic effect at all the combination of anoxic and insulin shock promises a more lasting and better effect with a single application than many repetitions of anoxic shock or insulin shock alone. This combination also has the great advantage that the insulin hypoglycemia has disappeared when anoxic shock begins, so that it cannot interfere with instantaneous resaturation of the tissues with oxygen whenever it may be necessary to interrupt the anoxic shock swiftly.

COMMENT

The danger of anoxemia is too well known from experience with carbon monoxide poisoning (Haldane,[25] Barcroft [42] and Henderson [43]) or from fatal incidents with nitrogen monoxide anesthesia (Courville [44]

40. von Schrötter, H.: Ueber Schädigungen des Organismus bei Verminderung des äusseren Luftdruckes, Verhandl. d. deutsch. path. Gesellsch. **5**:410, 1902.

41. Rosin, A.: Morphologische Organveränderungen beim Leben in Luftverdünnung, Beitr. z. path. Anat. u. z. allg. Path. **76**:153, 1926.

42. Barcroft, J.: Anoxemia, Lancet **2**:485, 1920.

43. Henderson, Y.: The Pharmacopeia and the Physician: Respiratory Stimulants and Their Uses, J. A. M. A. **108**:471 (Feb. 6) 1937.

44. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129, 1936.

and Steegmann [45]) to be overlooked. There is, however, a decisive difference between anoxic shock and anoxemia in the conditions just mentioned. After termination of anoxic shock, instantaneous resaturation of the blood with oxygen is possible, and within a few seconds oxygen is again available for the tissues. This is not the case after carbon monoxide poisoning, since its removal from the hemoglobin requires valuable time, during which the oxygen supply to the tissues continues to remain insufficient, so that damage of the tissue may occur and perhaps become irreversible. The high solubility of nitrogen monoxide in plasma, which is many times higher than that of oxygen or nitrogen (Wieland,[46] Seevers and Waters [47]), may play a similar delaying role in the resaturation of the tissues with oxygen. This is especially dangerous if anoxia has already reached a critical point when the anesthesia is interrupted. Aside from this, there are definite reasons for thinking that anesthetics may have a histotoxic effect on brain cells. Jowett and Quastel [48] have shown that several anesthetics and narcotics depress oxidative processes in brain tissue, even in concentrations not higher than those reached during actual anesthesia. Studies of Wortis [11] and Henderson [43] pointed in the same direction, and Hartman [49] described even anatomic changes resembling anoxic lesions in the brain after sedatives had been taken. With respect to these studies, combined anoxic shock and administration of any anesthetics, narcotics or sedatives cannot be considered advisable as long as no such drug is known the effect of which can be interrupted as swiftly as that of simple anoxic shock alone.

If, however, for any clinical reason, a sedative should be required before the induction of anoxic shock, it is recommended that insulin in a moderate, subconvulsive dose be administered about three hours prior to anoxic shock. With this arrangement, a sedative effect may be procured without any possible interference of the drug with instantaneous resaturation of the blood and the tissues with oxygen after termination of the subsequent anoxic shock. It is only the insulin hypoglycemia that affects the brain, according to facts established thus far, and this hypoglycemia is already receding spontaneously when the anoxic shock

45. Steegmann, A. T.: Encephalopathy Following Anesthesia, Arch. Neurol. & Psychiat. **41**:955 (May) 1939.

46. Wieland, H.: Ueber den Wirkungsmechanismus betäubender Gase, des Stickoxyduls und des Azetylens, Arch. f. exper. Path. u. Pharmakol. **92**:96, 1922.

47. Seevers, M. H., and Waters, R. M.: Pharmacology of the Anesthetic Gases, Physiol. Rev. **18**:447, 1938.

48. Jowett, M., and Quastel, J. R.: The Effects of Narcotics on Tissue Oxidations, Biochem. J. **31**:565, 1937.

49. Hartman, F. W.: Some Etiological Factors and Lesions in Cerebral Anoxia, Am. J. Clin. Path. **8**:629, 1938.

is induced three hours later. Moreover, the gradually ensuing anoxic hyperglycemia definitely neutralizes the hypoglycemia, so that it has vanished long before the anoxic shock approaches its peak.

The report of Binet, Strumza and Ordonez [50] that during experiments on anoxia in dogs standstill of the heart frequently occurred prior to the arrest of respiration is confirmed by experiments on rabbits, with my arrangement, merely under the condition that definite weakening of the heart was produced prior to the anoxic shock by preexisting cardiac disease, by frequently repeated anoxic shocks without sufficient intervals of rest or by preceding injections of large shock doses of insulin. In healthy rabbits slowly oncoming paralysis of the respiratory center was easily recognizable at least one or two minutes prior to standstill of the heart. In possible tests on patients, a close surveillance of the heart action, however, is indispensable.

If anoxic shock is recommended as a therapeutic method because of the similarity of its symptoms and the changes produced in the tissue to those elicited by insulin shock, the question arises how the favorable therapeutic effect of insulin shock is brought about. Gellhorn [17] recently has endeavored to bring to a common denominator the favorable therapeutic results of Sakel's insulin shock, Meduna's metrazol treatment, treatment with sodium cyanide (Loevenhart), anesthesia of long duration, or *Dauerschlaf* (Kläsi), and anoxia. He maintained that all these procedures produce directly or indirectly an anoxic state in the brain, which reactively causes stimulation of the sympathicoadrenal system. It had previously been shown (Singer [51]) that in schizophrenia the reactivity of the sympathicoadrenal system was lower than normal. Gellhorn thus concluded that the essential curative factor of all the procedures mentioned was lasting stimulation of the sympathicoadrenal system elicited by anoxia of the brain.

It seems still questionable, however, whether the low reactivity of the sympathicoadrenal system is more than a concomitant feature of schizophrenia, both conditions perhaps being dependent on disturbances in the brain, possibly in the hypothalamus. Thus it seems worth while to emphasize some anatomic facts established. Experimental studies on insulin shock, as well as observations on persons who died of insulin hypoglycemia (resulting from overdoses of insulin in treatment of diabetes, insulin shock therapy or adenoma of pancreatic islets [52]), have shown that frequent insulin shocks, like those employed in the successful

50. Binet, L.; Strumza, M. V., and Ordonez, J. H.: Cœur et anoxie, Arch. d. mal. du cœur **31**:11, 1938.

51. Singer, H. D.: Psychosis and the Central Autonomic Nervous System, J. A. M. A. **110**:2048 (June 18) 1938.

52. Baker, A. B.: Cerebral Damage in Hypoglycemia: A Review, Am. J. Psychiat. **96**:109, 1939.

treatment of schizophrenia, bring with them destruction of single or more numerous neurons in various parts of the brain. The same has been observed in cases of epilepsy (Spielmeyer,[53] Scholz [54] and Müller [55]), which, according to Meduna,[56] is rarely coincident with schizophrenia, and also after metrazol treatment (Weil and Liebert [57]). According to the findings of Hartman, the same can be expected to occur after *Dauerschlaf* therapy with narcotics and sedatives. After anoxic shock we have found corresponding changes in the brain (fig. 5). Büchner and Luft [58] described degenerative changes in ganglion cells around the fourth ventricle, in the medulla oblongata and in the cerebellum of animals which for about a hundred hours were exposed to severe anoxemia, until they died. The characteristic feature of all these changes is that only single neurons are eliminated on a more or less large scale, and not entire nuclei or larger areas in a particular region of the brain. Thus, lasting loss of important functions has in general not been observed, and the elimination of single neurons need, obviously, not be considered particularly dangerous. Cobb [59] suggested that there is a great reserve of neurons that is probably not called on for ordinary mental activity. Thus, it can be considered established that a more or less widespread "microresection" of brain tissue is unintentionally accomplished by the successful therapeutic measures mentioned. This seems to be the prerequisite of a favorable therapeutic result by these methods. In this connection, it is also of interest that Egas Moniz and Almeida Lima [60] and Freeman and Watts [61] have recently reported favorable

53. Spielmeyer, W.: The Anatomic Substratum of the Convulsive State, Arch. Neurol. & Psychiat. **23**:869 (May) 1930.

54. Scholz, W.: Ueber die Entstehung der Hirnbefunde bei Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **145**:471, 1933.

55. Müller, G.: Zur Frage der Altersbestimmung histologischer Veränderungen im menschlichen Gehirn unter Berücksichtigung der örtlichen Verteilung, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:1, 1930.

56. von Meduna, L.: Die Bedeutung des epileptischen Anfalles in der Insulin und Cardiazolbehandlung der Schizophrenie, Psychiat.-neurol. Wchnschr. **39**:331, 1937.

57. Liebert, E., and Weil, A.: Histopathologic Changes in the Brain Following Injections of Metrazol, Arch. Neurol. & Psychiat. **42**:690 (Oct.) 1939.

58. Büchner, F., and Luft, U. C.: Hypoxämische Organveränderungen besonders des Centralnervensystems, Klin. Wchnschr. **15**:213, 1936. Luft, U. C.: Irreversible Organveränderungen durch Hypoxämie im Unterdruck, Beitr. z. path. Anat. u. z. allg. Path. **198**:323, 1937.

59. Cobb, S.: Review of Neuropsychiatry for 1937, Arch. Int. Med. **60**:1098 (Dec.) 1937.

60. Egas Moniz and Almeida Lima: Premiers essais de psychochirurgie; technique et résultats, Lisboa méd. **13**:152, 1936.

61. Freeman, W., and Watts, J. W.: Prefrontal Lobotomy in the Treatment of Mental Disorders, South. M. J. **30**:23, 1937.

results in the treatment of certain psychotic conditions after resection of twelve small pieces of brain tissue, and it might well be conjectured that the occasionally observed curative effect of highly febrile diseases on schizophrenia (Wagner von Jauregg [20]) depends on the destruction of

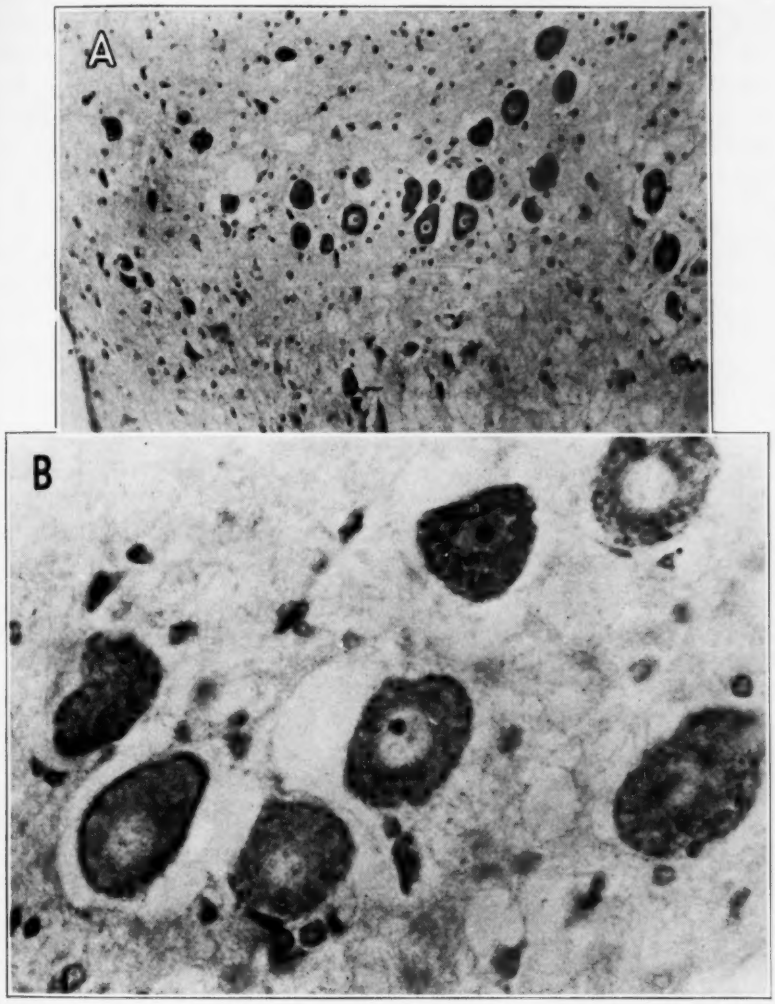

Fig. 5.—*A*, a nucleus at the floor of the fourth ventricle composed of large ganglion cells, the Nissl flakes of which are in various degrees broken down to dustlike formations. The rabbit had been subjected to three anoxic shocks on one day, each extended to the limit. The periods of rest between shocks were fifteen minutes each. The last shock was extended until the respiration ceased, two minutes after onset of gasping respiration. Short artificial respiration revived the rabbit, and it was killed twenty-four hours later. *B*, higher magnification of several ganglion cells.

some neurons in the brain by these diseases. Hartman and Major [62] have recently described such lesions in artificially produced febrile conditions and expressed the opinion that they were similar to those produced by anoxia. It is still too early to discuss in detail how these anatomic lesions bring about the improvement of the former psychotic condition. The general functional readjustment of the central nervous system that follows multiple microdestruction of brain tissue may bring with it the favorable change. Substances absorbed at the many small foci of degenerating neurons may play an essential part eventually by their effect on the sympathicoadrenal system.

SUMMARY

Results of animal experiments are presented as a basis for a feasible treatment of schizophrenia by anoxia, the particular procedure being briefly denoted as anoxic shock. After termination of the shock at its peak, twitchings and even violent seizures of short duration may occur, characteristically after resaturation of the blood with oxygen.

Preexisting cardiac diseases, frequent repetitions of anoxic shock without sufficient rest between or a combination of the shock with administration of anesthetics or sedatives increases the risk of the method considerably.

Combination of anoxic shock with administration of moderate, subconvulsive doses of insulin from three to five hours prior to its induction enhances the effect on the brain without increasing the risk of the shock, and is considered a promising therapeutic method. Combined anoxic shock and administration of insulin in real shock doses, however, is dangerous.

The common therapeutic factor of the various modern shock and drug therapies for schizophrenia is held to be the general functional readjustment of the central nervous system after the multiple microdestruction of brain tissue that is unintentionally accomplished by all these methods.

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62. Hartman, F. W., and Major, R. C.: Pathologic Changes Resulting from Accurately Controlled Artificial Fever. Am. J. Clin. Path. **5**:392. 1935.

News and Comment

POSTGRADUATE INSTITUTE ON PSYCHIATRY FOR STATE HOSPITALS

The first postgraduate institute on psychiatry for state hospitals was held at Agnews State Hospital, Agnew, Calif., June 17 to 29, 1940. The institute was attended by 35 physicians. Each state hospital in California was represented by one or more physicians, as well as by physicians from Montana, Arizona and Utah. The faculty at this institute consisted of Dr. Spafford Ackerly, Dr. Karl Neubuerger, Dr. Wendell Muncie, Dr. Frederick Parsons, Dr. Walter Treadway, Dr. Mark Gerstle Jr., Dr. Robert Stone, Dr. David O. Harrington, Dr. Aaron Rosanoff, Dr. Jacob Kasanin, Dr. J. P. Frostig and Dr. Charles A. Rymer, who served as coordinator of the institute.

The institute was sponsored by the American Psychiatric Association through its Committee on Psychiatry in Medical Education, and was financed by the Rockefeller Foundation. The purpose of the institute was to offer to its members not only a consideration of the newer methods in neuropsychiatric practice but also a critical review of the accepted practices now in use. For this purpose, lectures were offered in psychobiology, psychopathology, clinical psychiatry, clinical neurology, psychotherapy, neuropathology administrative psychiatry, neuro-ophthalmology, neuroroentgenology, psychoanalysis, psychiatry and the Rorschach and new technics in neuropsychiatry. In addition to these, one lecture was open to the public and another was given at a joint meeting with the County Medical Society. These two meetings were well attended.

Great enthusiasm was displayed by the physicians enrolled, who expressed a definite desire to establish a yearly institute patterned after the first. It was generally accepted that the institute offered a splendid opportunity to prepare for certification by the American Board of Psychiatry and Neurology.

The next institute is scheduled to be held in Lakeland, Ky., Sept. 23 to Oct. 6, 1940.

Case Reports

BEHAVIOR OF ELECTROLYTES IN FAMILIAL PERIODIC PARALYSIS

JOSEPH W. FERREBEE, M.D.; MILDRED K. GERITY, M.A.; DANA W. ATCHLEY, M.D., AND ROBERT F. LOEB, M.D., NEW YORK

Familial periodic paralysis is a rare but well recognized syndrome in which periods of extensive flaccid motor paralysis alternate with periods of normal health. The only regularly observed fault is a periodic disturbance in the internal distribution of potassium,[1] believed by certain workers to be related to the movements of potassium that accompany carbohydrate metabolism.[2] The paralytic symptoms are associated with a temporary decrease in serum potassium concentration and can be alleviated by the administration of potassium salts.[3] In the opinion of Pudenz, McIntosh and McEachern [1a] the efficacy of this treatment does not depend on changes in the serum potassium concentration or on changes in the potassium content of the muscles. Their experiments have indicated that the effect of potassium is mediated in some way through the central nervous system. In the following study evidence is presented to show that there is a disturbance in the internal distribution of potassium, with associated changes in the renal excretion of potassium and a number of other electrolytes. In addition, observations are described which fail to confirm the view of Pudenz, McIntosh and McEachern that the effect of potassium is mediated through the central nervous system.

From the Departments of Medicine and Neurology, Columbia University College of Physicians and Surgeons; the Presbyterian Hospital, and the Neurological Institute of New York.

1. (*a*) Pudenz, R. H.; McIntosh, J. F., and McEachern, D.: Rôle of Potassium in Familial Periodic Paralysis, J. A. M. A. **111**:2253 (Dec. 17) 1938. (*b*) Ferrebee, J. W.; Atchley, D. W., and Loeb, R. F.: A Study of the Electrolyte Physiology in a Case of Familial Periodic Paralysis, J. Clin. Investigation **17**:504, 1938. (*c*) Allott, E. N., and McArdle, B.: Further Observations on Familial Periodic Paralysis, Clin. Sc. **3**:299, 1938. (*d*) Gammon, G. D.; Austin, J. H.; Blithe, M. D., and Reid, C. G.: The Relation of Potassium to Periodic Family Paralysis, Am. J. M. Sc. **197**:326, 1939.

2. Aitkin, R. S.; Allott, E. N.; Castleden, L. R. M., and Walker, M.: Observations on a Case of Familial Periodic Paralysis, Clin. Sc. **3**:47, 1937. Allott and McArdle.[1c]

3. Our patient has been taking 30 Gm. of potassium chloride daily for the past eighteen months. This therapy has enabled him for the first time in his life to carry on normal activity. He has missed but one day's work in this period and has remained in excellent general health. Since the potassium chloride is mostly taken with his meals, he still has severe attacks in the early morning, but by taking 10 Gm. of potassium chloride in a glassful of water before breakfast he is consistently able to arrive at work on time.

REPORT OF A CASE

Experimental Method.—The patient,[4] a healthy, intelligent unmarried man aged 30, was confined during the periods of the balance studies to the metabolism ward of the Presbyterian Hospital, where he was maintained on a constant ambulatory regimen. A night seldom passed without his having some motor weakness, and a month rarely went by without the occurrence of one or two major episodes, during which for from twelve to thirty-six hours there was almost complete paralysis of the voluntary muscles except those of the face, pharynx and diaphragm.

The dietary intake of sodium, potassium, chloride, calcium, nitrogen and water was determined in five day periods by analyses of duplicate diets. Urine and stools were also analyzed in five day periods, and on occasion analyses of urinary outputs were made over shorter periods, including, in addition to those of the previously mentioned substances, determinations of creatine, creatinine, magnesium, phosphate, ammonia and hydrogen ion concentration. The total extracellular fluid volume,[5] circulating plasma volume,[5] hematocrit reading, erythrocyte count, potassium concentration of whole blood and sodium, potassium, calcium, magnesium, chloride, inorganic phosphate, bicarbonate, dextrose, albumin and globulin, phosphatase and acetylcholine esterase contents of the serum were determined at various times. All analyses were made in duplicate, with current standard methods of analyses. The effect of severe attacks of paralysis on these measurements and on the various urinary outputs was observed. Studies were also made of the effect of the intake of large amounts of sodium and potassium salts on the frequency and severity of attacks and on the salt and water measurements. For purposes of comparison, the salt and water exchange was studied briefly in a normal medical student placed on a constant dietary regimen.

During paralytic attacks of varying intensity potassium chloride was injected into the antecubital vein of one arm, while circulation was stopped in the other arm by an arterial tourniquet (experiment of Pudenz, McIntosh and McEachern). The flexor muscles of the two forearms were observed for evidence of returning function, and the clinical observations were checked by electromyographic tracings, an ink-writing oscillograph with surface leads over the flexors of the fingers recording action potentials simultaneously produced in the two forearms by the patient's attempts to close his hands as tightly as possible.[6]

Results.—Sharp fluctuations in excretion of electrolytes associated with attacks of paralysis take place so rapidly that they may escape detection completely in analyses for five day periods (fig. 1). However, analyses covering periods of several days were of value in pointing out basic metabolic facts, such as the nitrogen equilibrium, the magnitude of the fecal excretion of water, nitrogen and electrolytes, the losses, due to respiration and insensible perspiration, the relation of sodium balance and water balance and the difference between the absorption

4. The case of this patient was reported and described as a classic instance of familial periodic paralysis (Zabriskie, E. G., and Frantz, A. M.: Familial Periodic Paralysis, Bull. Neurol. Inst. New York **2**:57, 1932).

5. Gregersen, M. I., and Stewart, J. D.: Simultaneous Determination of the Plasma Volume with T1824 and the "Available Fluid" Volume with Sodium Thiocyanate, Am. J. Physiol. **125**:142, 1939.

6. The electromyographic tracings were made at the Neurological Institute of New York under the direction of Dr. Paul Hoefer of the department of neurology, Columbia University College of Physicians and Surgeons.

and excretion of sodium and the absorption and excretion of potassium. Our data do not indicate that in these respects the patient differed greatly from the normal.

During the course of the experiment the patient's weight remained fairly constant, and nitrogen equilibrium was maintained within 2 Gm., usually less,

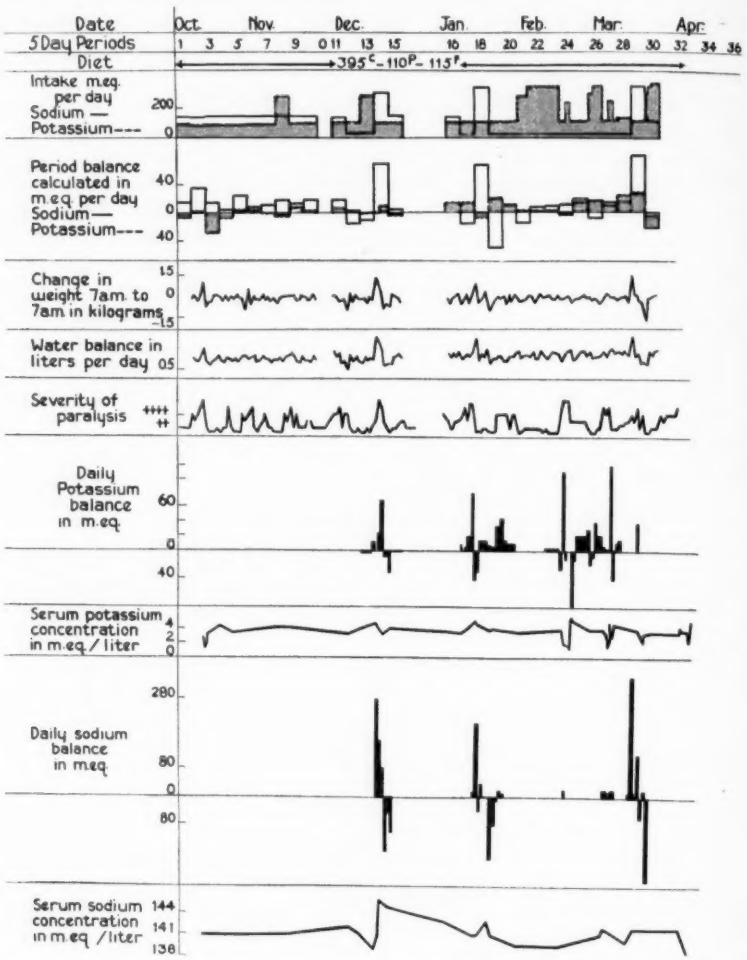

Fig. 1.—Relation of attacks to electrolyte balances, based on analyses for five day periods.

per day. The stools contained on an average per day about 40 to 150 Gm. of water, 1 to 2 Gm. of nitrogen, 10 to 30 milliequivalents of calcium, 0.3 to 4 milliequivalents of sodium and chloride and 10 to 20 milliequivalents of potassium. The higher values for sodium, chloride, potassium and water were found in the loose stools which appeared on the first days of the high potassium chloride intake. These amounts were all negligible when compared with the amounts

excreted in the urine except that in the case of calcium the fecal excretion was, as usual, about twice the urinary excretion.[7]

Except during prolonged attacks or sudden alterations in the intake of sodium chloride, analyses for the five day periods showed a positive sodium and chloride balance of approximately 20 milliequivalents per day, a relatively close potassium

TABLE 1.—*Relation of Sodium Balance, Water Balance and Extracellular Fluid Volume During Sudden Changes in Intake of Sodium Chloride in Patient with Familial Periodic Paralysis*

	December							January		March	
	11	12	13	14	15	16	17	15	16	11	12
Intake of sodium chloride, mEq. per day	21	309	309	309	309	309	140	26	368	29	369
Sodium balance, mEq. per day*	0	+258	+140	+61	−174	−84	−97	0	+200	0	+285
Change in body weight, Kg.	0	+1.4	+1.0	+0.2	−0.8	−0.5	−0.6	+0.3	+1.0	−0.3	+1.5
Change in urine volume, liters	0	−1.4	−1.3	−0.3	+0.5	+0.3	+0.3	−0.3	−1.3	0	−1.5
Change in extracellular fluid volume, liters (thiocyanate method)	0	+1.6	....	....	....	....	....	?	+1.3	?	+1.7
Change in extracellular fluid volume, liters (sodium method)†	..	+1.5	....	....	....	....	....	....	+1.3	....	+1.7
Blood serum volume, liters	2.7	3.3	....	....	....	....	....	....	....	....	....
Blood serum protein concentration, mg. per 100 cc.	6.4	5.9	5.6	....	....	6.4	....	7	6	6.1	5.8
Blood serum sodium concentration, mEq. per liter	139	141	146	....	....	145	....	141	141	140	142
Severity of paralysis	0	2+	6+	5+	2+	1+	0	5+	0	2+	3+

* Corrected for average insensible loss.
† Calculated as: sodium balance, in milliequivalents, minus (volume of extracellular fluid, in liters, times increase in sodium concentration) divided by final sodium concentration, in milliequivalents per liter, equals the increase in extracellular or sodium fluid volume.

TABLE 2.—*The Effect on Sodium Balance, Water Balance and Extracellular Fluid Volume of a Normal Student of a Sudden Change in Sodium Chloride Intake of from 30 to 330 Milliequivalents Per Day*

Sodium balance, mEq. per day	+240
Change in body weight, Kg.	+ 1.1
Change in urine volume, liters	− 1.1
Change in extracellular fluid volume, liters (thiocyanate method)	+ 1.1
Change in extracellular fluid volume, liters (sodium method)	+ 1.4

balance and a positive water balance of about 1.5 liters per day, with a total intake of 4.5 liters. These amounts probably represent the losses of these substances through perspiration and respiration.

As would be expected of a subject in caloric equilibrium, changes in water balance were closely followed by changes in weight. It was interesting to note a normal relation of sodium balance to water balance and extracellular fluid

7. The calcium balance was persistently negative, 3 to 6 milliequivalents per day, as has been the usual experience in this laboratory with patients restricted in activity.

volume, particularly when large alterations in the measurements were produced by sudden changes in the sodium chloride intake (tables 1 and 2). Large amounts of potassium chloride, 30 Gm. a day, were rapidly absorbed and equally rapidly excreted without affecting the potassium balance or altering the other experimental measurements in any way, but it required several days for urinary excretion to become adjusted to changes in the sodium chloride intake (fig. 1).

The amount of potassium chloride ingested had considerable effect on the frequency and severity of the attacks of paralysis (fig. 1). Daily determinations of potassium balance were made in an effort to understand the mechanism of this effect and the significance of the drop in serum potassium concentration that accompanied the attacks (figs. 1, 2 and 3). The disturbance in urinary excretion shown in these daily balances was not confined to potassium, contrary to our original impression. The extent of the disturbance in sodium excretion is apparent in the analyses for short time intervals (figs. 4, 5 and 6).

The rate of excretion of potassium in our patient varied greatly and did not follow the normal diurnal pattern even in periods of freedom from attacks (fig. 6*A*). A seizure was not preceded by an exceptional loss of potassium. Although there was occasionally an increase in potassium excretion prior to an attack, quantitatively similar increases were observed without the development of paralysis. In this connection it is interesting to note that the abnormally large excretion of potassium on the night of the control day was associated with a period of well-being and not with an attack of motor weakness. A marked decrease in potassium excretion always coincided with the paralysis and with the drop in serum potassium concentration (figs. 1, 4 5, and 6). Recovery was accompanied by a temporary increase in potassium excretion, during the course of which the potassium balance was partially regained.

During attacks, changes similar to those described for potassium occurred in the urinary excretion of sodium, chloride and phosphate (figs. 4, 5 and 6), but these changes could not be correlated with changes in the serum concentrations of these ions. No striking change in the sugar or the inorganic phosphate level of the blood was observed during a severe attack (figs. 2 and 3). Unfortunately, on only one occasion was the interpretation of changes in sodium and chloride concentrations of the serum not complicated by previous changes in sodium chloride intake (fig. 1). On this occasion the fall (2 milliequivalents) in sodium concentration that accompanied recovery was within the experimental error.

The excretion of nitrogen, creatinine and water was relatively unaffected by the attacks, and the excretion of creatine, though large (0.75 Gm. per day) and somewhat increased (20 to 50 per cent) during periods of severe seizures, was not closely related to the degree of paralysis (fig. 4).

The excretion of calcium and magnesium in the urine differed from that of the other substances determined in that it was increased at the onset of one acute attack and was consistently elevated throughout another. No accompanying changes in serum concentrations were found.

The excretion of ammonia, hydrogen ion concentration of blood and of urine, serum volume, extracellular fluid volume, hematocrit readings, erythrocyte count, erythrocyte potassium concentration and serum acetylcholine esterase were not found to be altered significantly by attacks of paralysis.

On the four occasions on which potassium chloride was injected intravenously during an attack, it was not possible to demonstrate recovery of muscle strength in an arm blocked from the general circulation by an arterial tourniquet, although recovery was apparent in the arm in which the injection was made and

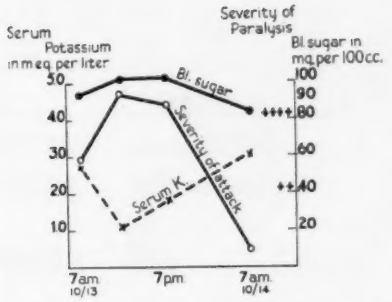

Fig. 2.—Relation of severity of paralysis, serum potassium concentration and blood sugar concentration.

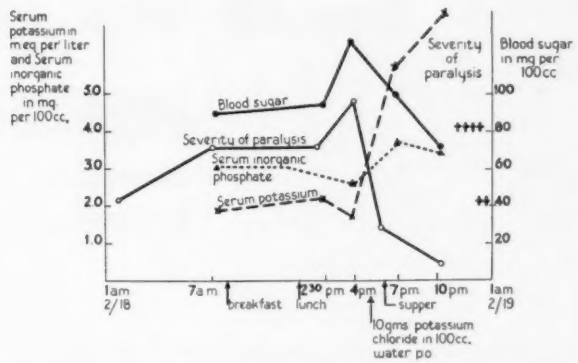

Fig. 3.—Relation of severity of paralysis, potassium and inorganic phosphate concentrations of the serum and sugar concentration of the blood.

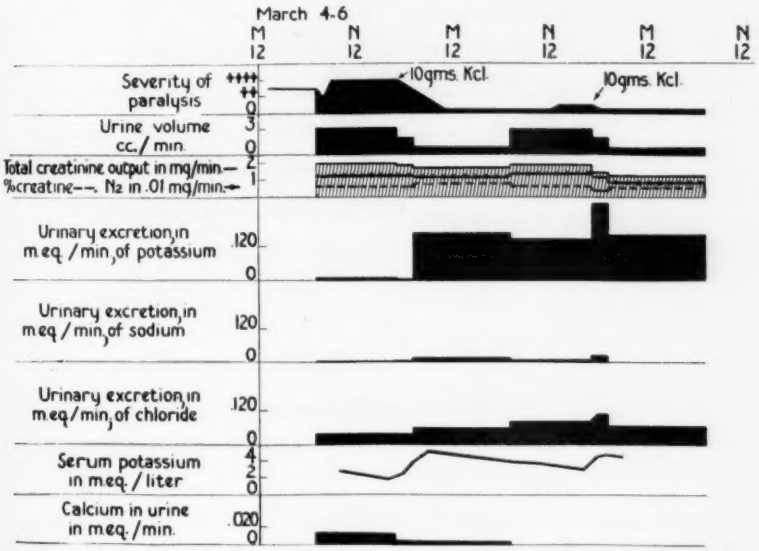

Fig. 4.—Fractional twenty-four hour excretion studies showing the changes associated with a severe attack of paralysis.

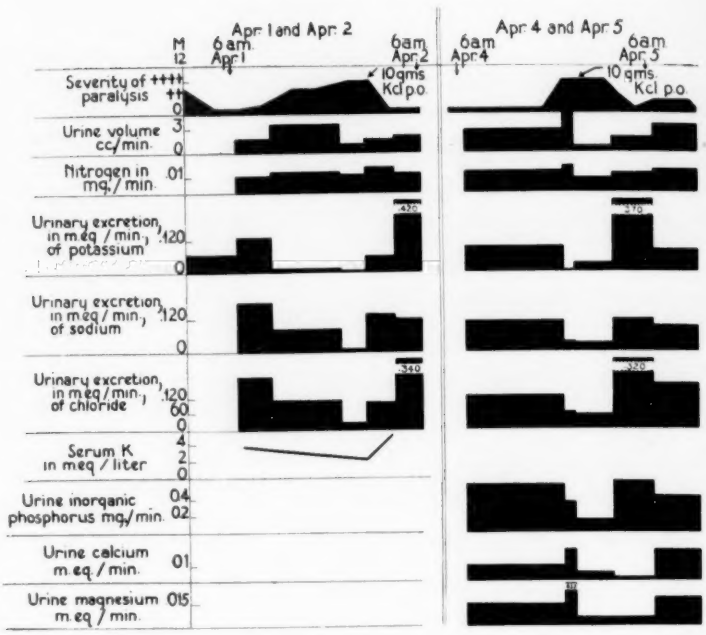

Fig. 5.—Fractional twenty-four hour excretion studies showing the changes associated with a severe attack of paralysis.

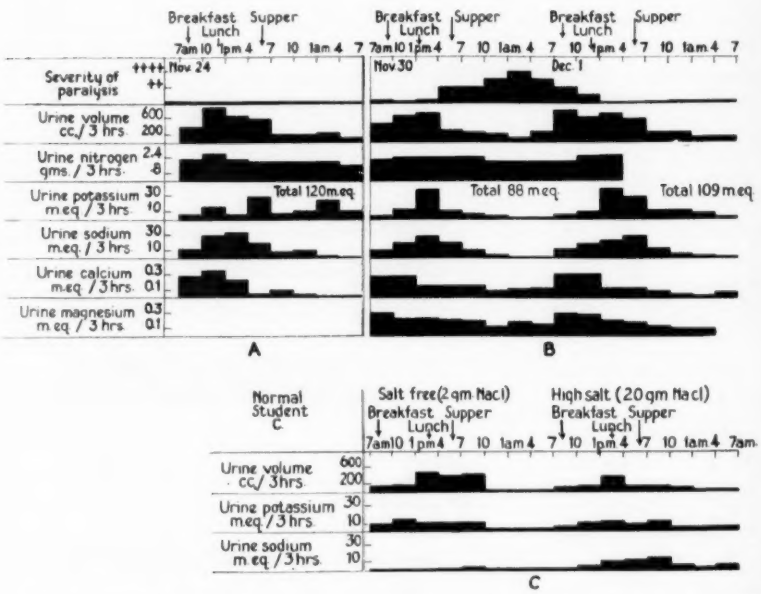

Fig. 6.—Studies of urinary excretion in three hour periods. *A*, patient during an interval free from attacks (no attacks for forty-eight hours preceding or following the control day); *B*, patient during a severe attack, and *C*, normal student on a standard diet.

in the rest of the body. It was found in control tests during 2 plus [8] and 3 plus attacks that application of an arterial tourniquet caused an actual loss of muscle power in the blocked arm after from thirteen to seventeen minutes. In order to obtain evidence of recovery before this tourniquet effect vitiated a comparison of the open and the blocked arm, it was necessary to carry out the experiment with the patient in a 2 plus attack and to inject a solution of potassium chloride (0.5 per cent potassium chloride in a 0.85 per cent solution of sodium chloride) to the limit of cardiac tolerance. As much as 1.5 Gm. of potassium chloride was given intravenously within the first five minutes of the experiment, and administration was continued at this rate, so that as a rule the patient had received 3 Gm. at the end of ten minutes and 4.5 Gm. at the end of fifteen minutes. As the electromyograms indicate (fig. 7), there was a return of muscle activity in the flexor muscles of the right forearm, which were open to the solution of potassium chloride, but no return in the flexors of the left forearm, which were blocked from the general circulation by an arterial tourniquet. This return of function began at about the sixth minute of injection and was obvious clinically as well as electromyographically. At the end of thirteen minutes, when 2.9 Gm. of potassium chloride had been injected (fig. 7*B*), there was a considerable increase in the strength of the right hand grip, whereas the left hand grip remained about as at the beginning of the experiment (fig. 7*A*). When the arterial tourniquet was removed from the left arm at the end of thirteen minutes, strength gradually returned in that arm, and eight minutes later strength in the two arms was relatively comparable (fig. 7*C*).

COMMENT

The observations described in this paper and the experiences reported by other groups of investigators make clear the existence of several peculiarities in the potassium metabolism of patients afflicted with familial periodic paralysis. Spontaneous attacks of paralysis are associated with a temporary decrease in serum potassium concentration and almost complete disappearance of potassium from the urine. Since no exceptional increase in potassium excretion immediately precedes these attacks, the sudden disappearance of potassium from the serum and from the urine probably does not represent a depletion of the stores of potassium in the body. The increased excretion of potassium which follows a seizure is more compatible with the assumption that a transitory retention of potassium by the tissues reduced the amount of circulating potassium. This alternate retention and release of potassium continues during periods of well-being (fig. 6*A*), and suggests that the abnormality of potassium metabolism in these patients is not limited to the periods of actual paralysis.

Whether the persistent creatinuria and the changes in the excretion of sodium, chloride, calcium, magnesium and phosphate which accompany attacks are related to the underlying metabolic disturbance or are secondary phenomena dependent on the disturbance in regulation of potassium metabolism we cannot at present determine. The absence of any relation between the frequency of paralytic seizures and the intake

8. A 2 plus attack is the arbitrary designation for one in which the patient can no longer turn over in bed, is just able to open and close his hands and has an almost imperceptible grip.

of sodium and the apparently normal relation between sodium balance and water balance incline us to doubt that the sodium metabolism of these patients is primarily affected. The changes in the excretion of calcium and magnesium found in our patient, while in agreement with those reported in the earlier work of Shinosaki,[9] are much less striking and are not sufficient to permit interpretation. A parallelism between the excretion of potassium and that of inorganic phosphate has been reported in patients with familial periodic paralysis by Allott and McArdle.[1c] Our limited experience confirms the findings of these

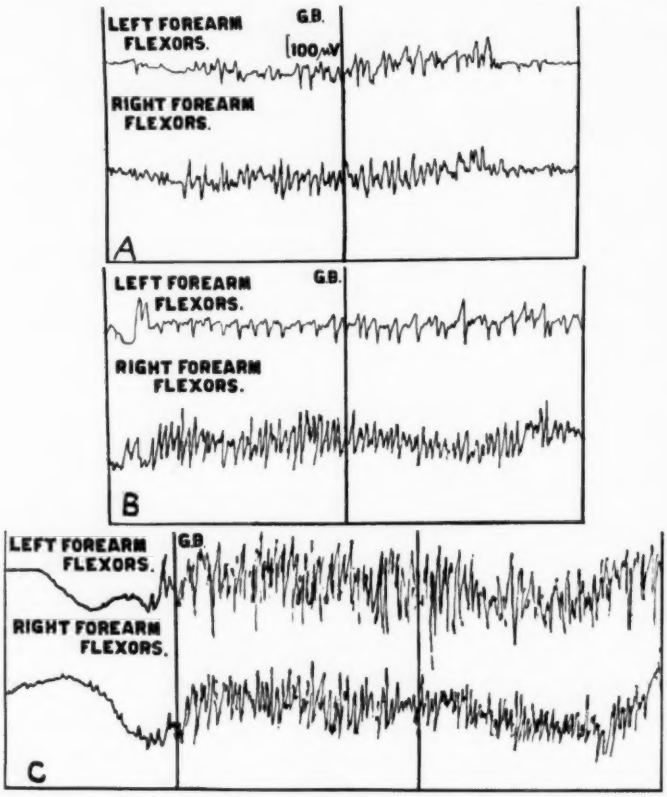

Fig. 7.—Electromyographic tracings of recovery of muscle function during intravenous administration of a solution of potassium chloride. *A*, taken at beginning of the experiment, before injection of potassium. The hand grips are equally weak on the two sides. *B*, taken thirteen minutes later, after injection of 2.9 Gm. of potassium chloride into the right antecubital vein, with the left arm blocked by an arterial tourniquet maintained at a pressure of 200 mm. of mercury. The right hand grip is much stronger than the left and shows improvement over that in *A*. *C*, taken eight minutes after *B* and removal of the arterial tourniquet from the left arm. The hand grips are relatively equal on the two sides.

9. Shinosaki, T.: Klinische Studien über die periodische Extremitätenlähmung, Ztschr. f. d. ges Neurol. u. Psychiat. **100**:564, 1926.

investigators. It is worth pointing out that the changes in urinary excretion probably do not represent a failure of renal function, since the excretion of nitrogen, creatine, creatinine and water remains relatively unaffected during paralysis.

Normal persons experience no motor symptoms when the serum potassium concentration is reduced by injection of dextrose, insulin, epinephrine or desoxycorticosterone,[10] and in patients with familial periodic paralysis there is not a consistent relation between the severity of the paralysis and the extent to which the potassium concentration of the serum is lowered. The report by Pudenz, McIntosh and McEachern that a small intravenous injection of potassium chloride may restore muscle power without raising the potassium concentration of the serum appears to be a further argument against the importance of the potassium concentration of the serum as a specific determinant of muscular irritability. In our patient the correlation between paralysis and serum potassium concentration during the untreated spontaneous attacks may have been dependent on the fact that his attacks occurred while he was on a rigidly constant regimen. Under these standard conditions the serum potassium concentration may have served as a more accurate index of the extent to which the internal distribution of potassium was altered than in those instances in which attacks have been artificially induced.

The effectiveness of potassium salts in preventing and relieving paralysis suggests that the disappearance of potassium from the serum during attacks is associated with an increased need for potassium in certain tissues. The frequent occurrence of attacks at 3 or 4 a. m. is consistent with this view and may be related to the fact that dietary potassium is normally absorbed and excreted rapidly, leaving no supply of potassium with which to combat an abnormal demand when it occurs in the early morning hours. In a similar manner, the frequency with which attacks follow large carbohydrate meals or the injection of dextrose, insulin or epinephrine may depend on the decrease in available potassium which accompanies certain phases of carbohydrate metabolism. It does not necessarily follow that the effectiveness of these measures in inducing attacks of paralysis indicates abnormal carbohydrate metabolism in patients with familial periodic paralysis. As a matter of fact, in our experience with spontaneous attacks such changes as were found in the sugar and inorganic phosphate concentrations of the serum were compatible with the usual diurnal variations related to the ingestion of food (fig. 3).

At present it is not possible to define the derangement of metabolism responsible for the peculiar behavior of electrolytes, particularly potassium, in patients with familial periodic paralysis. Neither the locus of this disturbance, whether nervous, visceral, endocrine or muscular, nor its mode of action in affecting potassium distribution is known. Equally lacking is knowledge concerning the mechanism whereby the change in

10. Desoxycorticosterone in large subcutaneous doses given over a period of several days may cause muscular weakness in normal dogs, which can be relieved by the administration of potassium salts (Kuhlmann, D.; Ragan, C.; Ferrebee, J. W.; Atchley, D. W., and Loeb, R. F.: Toxic Effects of Desoxycorticosterone Esters in Dogs, Science **90**:496, 1939).

distribution of potassium within the body causes loss of the direct and indirect electrical excitability of the muscles. Inability to confirm in our patient the experience of Pudenz, McIntosh and McEachern leaves us no particular reason for implicating the nervous system in a discussion of the therapeutic action of potassium salts, and it seems that such discussion must await further electrical and chemical studies of the motor unit in patients with this disease.

SUMMARY

The disturbances in metabolism occurring in familial periodic paralysis were studied by placing a patient with this disorder under a controlled regimen and observing the alterations in urinary excretion and composition of the blood serum which accompanied spontaneous attacks of paralysis.

Loss of muscular irritability was found to be associated with a drop in serum potassium concentration and a marked decrease in the urinary excretion of potassium. Although there was occasionally an increase in potassium excretion prior to an attack, quantitatively similar increases were observed without the development of paralysis. Consequently it seemed fair to assume that the drop in serum potassium was not dependent on exceptional excretion of potassium.

Spontaneous recovery of motor function coincided with a return of serum potassium concentration toward normal and was followed by an increase in potassium excretion which partially restored the potassium balance.

Changes similar to those described for potassium occurred in the urinary excretion of sodium chloride and inorganic phosphate but were not accompanied by demonstrable changes in the serum concentration of these ions.

The changes in urinary excretion did not represent a general failure of renal function so far as could be determined by the excretion of water, nitrogen, creatine and creatinine, which remained relatively unaffected during paralysis.

Persistence of creatinuria and erratic fluctuations in potassium excretion throughout periods of well-being indicated that the essential abnormality of metabolism was not restricted to the periods of actual paralysis.

Electromyographic studies were made of the return of muscle function which followed the intravenous injection of a solution of potassium chloride. These studies failed to indicate that the therapeutic action of potassium salts was mediated through the central nervous system.

FAMILIAL PAROXYSMAL CHOREOATHETOSIS

Preliminary Report on a Hitherto Undescribed Clinical Syndrome

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The following case represents what is believed to be a hitherto undescribed clinical syndrome. The characteristic features of the syndrome are the paroxysmal occurrence of the attacks and the rich familial background. The patient presenting this syndrome was studied intensively at the Neurological Institute of New York from Nov. 3, 1938 to Jan. 19, 1939. During this period he was seen by most of the members of the staff, none of whom had seen a similar condition. A careful and meticulous review of the literature failed to reveal a case of a comparable syndrome.

REPORT OF A CASE

The patient was a white man aged 23, a textile worker, whose chief complaint was "spells," which had had their onset in infancy. He described them as of two types—"large" and "small". By this terminology he differentiated the severity and the duration of the attacks. Both types were preceded by an aura consisting of a tired feeling, stuffiness in the chest and throat and "a feeling as if the collar and belt are too tight." The aura was followed by "a quick drawing up" of the arm on either side, and occasionally of both arms simultaneously. This "drawing up" of the arms, as demonstrated by the patient, consisted of adduction of the arm at the shoulder and flexion at the elbow and wrist. At the same time there were slow, purposeless movements of the fingers in the form of irregular flexion, extension and spreading. The "drawing up" of the arm was usually associated with supination of the foot of the same side, making the patient's gait awkward and clumsy. He occasionally experienced diplopia and blurring of vision. The small attacks lasted from five to ten minutes. If they continued beyond this period a "large" attack ensued. The latter incorporated the following additional components: extension of the head, turning of the eyes upward and contraction of the facial muscles on the same side as the participating arm and leg. The muscles involved could sometimes be relaxed for a second or two but returned to their former state. The major attacks lasted for as long as two hours. During the minor attacks the patient had no difficulty in speaking, but during the "large" attacks his speech was dysarthric and at times anarthric. At no time did he fail to comprehend what was said to him, nor did he have any difficulty in elaborating his thoughts except for impairment of the peripheral speech musculature. There had never been loss of consciousness, biting of the tongue, bodily injury or loss of sphincter control during these attacks.

The attacks occurred most frequently just before, during or immediately after lunch. If he did not eat at noon, he might not have his first attack until about 4 p. m. The seizures then recurred just before, during or immediately after dinner. He occasionally had an attack in the evening. He was certain to have one if he drank a cocktail after dinner. The attacks never occurred during sleep, and they did not appear before lunch. He had more seizures on days when he

From the Department of Neurology, the Neurological Institute of New York.

drank coffee, tea, alcohol or coca cola. Fatigue, concentration or exposure also seemed to be precipitating factors. He had an average of one "large" and two "small" attacks a day. He learned that attacks ceased more quickly when he lay down, and if he was able to go to sleep, even for a few seconds, the seizure had disappeared when he awakened.

Family History.—A careful and detailed investigation was made of the patient's ancestors (fig. 1). There are 20 relatives who have the attacks at present; 7 others had the attacks from infancy until death. Seventeen were males and 10 females. The disease had its origin over one hundred years ago, with the patient's great-grandfather, who died at the age of 87. There were 6 children born to this great-grandfather. Two male and 2 female members suffered from the condition, among them the patient's grandfather. Two females were free of attacks. The patient's mother and his only sister were affected. There were 2 brothers who began to have attacks at the age of 3 or 4 months and who died at the ages of 12 and 14 months, respectively. One living brother has never been similarly affected. Through another branch of the family the attacks passed for five generations. The maternal grandfather died of Bright's disease and diabetes. The patient's mother has diabetes.

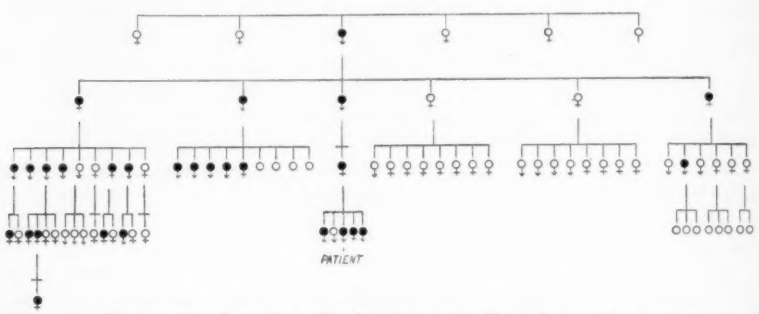

Fig. 1.—Chart showing the distribution of affected members through five generations; the black circles represent those involved.

The past history of the patient was without significance, except for measles at the age of 17.

Physical Examination.—The temperature was 99 F. (rectally), the pulse rate 84, the respiratory rate 22 and the blood pressure 122 systolic and 80 diastolic. His weight was 133 pounds (60.3 kg.) and his height, 5 feet, 10 inches (177.8 cm.). The patient was thin and asthenic, with blue eyes, light hair and many small, dark pigmented areas over the body. The cranium was normal in size and shape. The Macewen sign was not elicited, and auscultation of the skull gave negative results. Slight tenderness was present on palpation over the spinous processes of the first and second thoracic vertebrae. There were a few small discrete axillary and inguinal lymph nodes. The chest, heart and abdomen were normal. Rectal examination gave normal findings. Pes cavus was present bilaterally.

Neurologic Examination.—The patient was right handed; his gait and station were normal. No abnormal involuntary movements were observed except during an attack. Muscle status and strength were normal. Nonequilibratory coordination tests gave normal results. The reflexes were within normal limits. Test acts and speech were normal. There was a variable and inconstant short sock and long glove type of hypalgesia, hypesthesia and hypothermesthesia. The cranial nerves were intact. Mental examination gave normal results.

Laboratory Tests.—A blood count showed 88 per cent hemoglobin, a color index of 0.91, 4,700,000 red cells and 9,150 white cells per cubic millimeter, with a differential count of 59 per cent polymorphonuclear leukocytes, 38 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophils. Slight anisocytosis was present. Chemical examination of the blood showed: 11.1 mg. of urea nitrogen; 81 mg. of sugar; 10.2 mg. of calcium; 3.6 mg. of phosphorus and 2.8 Bodansky units of phosphatase, per hundred cubic centimeters. On fasting for twenty-four hours 83 mg. of sugar per hundred cubic centimeters was found. A Kline test of the blood gave negative results. The results of a dextrose tolerance test were: one-half hour, 135 mg.; one hour, 66 mg.; two hours, 56 mg.; three hours, 86 mg., and four hours, 57 mg., per hundred cubic centimeters.

Urinalysis revealed an alkaline reaction, a specific gravity of 1.026, no casts, no albumin and no sugar.

Examination of the spinal fluid on November 10 showed 2 cells per cubic millimeter and 32 mg. of protein per hundred cubic centimeters. The reaction for globulin was negative, and the colloidal gold curve was 1100000000. The Wassermann reaction was negative. On November 23 there were 5 cells per

Blood Electrolyte Partition

		Serum Carbon Dioxide		Chlorides				
		Volume, per Cent	Milli-equivalents per Liter	Milligrams per 100 Cc.	Milli-equivalents per Liter	Calcium	Sodium, Milli-equivalents per Liter (Calculated)	Potassium
November 11	Fasting	59.0	26.5	585.0	99.6	9.7	136.1	4.1
November 12	Early in attack	59.0	26.5	285.5	99 6	9.7	136.1	...
November 18	During attack	59.0	26.5	565.0	96.9	...	133.4	...
	Following attack	64.6	29.0	540.0	92.5	...	131.5	...

cubic millimeter and 29 mg. of protein per hundred cubic centimeters. The reaction for globulin was negative. The Wassermann reaction was negative, and the colloidal gold curve was normal.

The basal metabolic rate was —23 per cent.

Special Examinations.—A roentgenogram of the skull showed no evidence of pathologic change. Encephalograms showed that the occipital horns were slightly asymmetric; this was probably of no clinical significance. There was no other evidence of abnormality. The only indication of abnormal brain waves was the appearance of potentials with a frequency of 3 and 6 per second after hyperventilation, similar to those found in patients with epilepsy.

Consultations.—Psychiatric: An interview showed the patient to be pleasant, placid and cooperative. He did not seem to be neurotic, and his attacks apparently were not precipitated by emotional situations.

Ophthalmologic: The visual fields, visual acuity and optic fundi were normal. Slit lamp examination showed an atypical Kayser-Fleischer ring.

Neuro-Otologic: The cochlear and vestibular reactions were normal.

Psychologic: A Stanford-Binet test showed his mental age to be 15 years and 11 months and his intelligence quotient 1.06. The Arthur test gave a mental age of 15 years and 7 months. The impression was that of high average general intelligence and an average manual skill.

Course.—During the patient's hospitalization he was observed in many attacks. Each seizure was preceded by the aura previously described. The attacks started

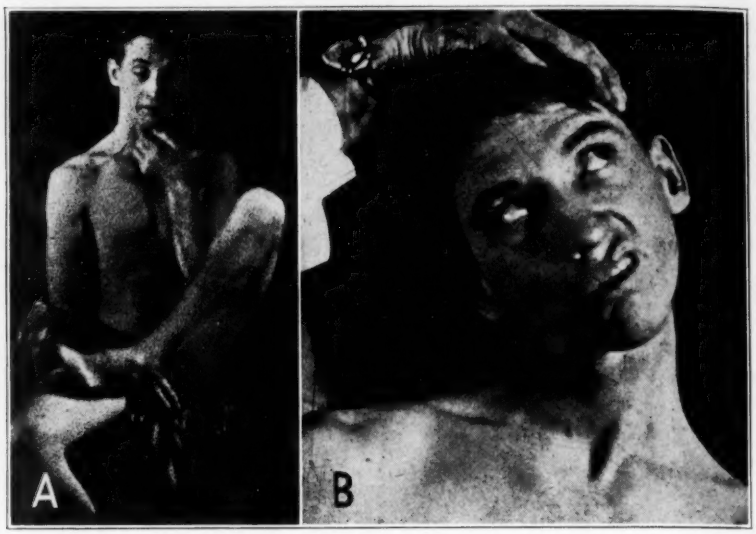

Fig. 2.—Patient during an attack induced by alcohol. *A*, supination of the left foot, flexion and external rotation of the left thigh, flexion of the left leg, adduction and internal rotation of the left arm and flexion of the left arm at the elbow. *B*, grimacing, primarily on the left side, torticollis and external and superior conjugate deviation of the eyes to the left.

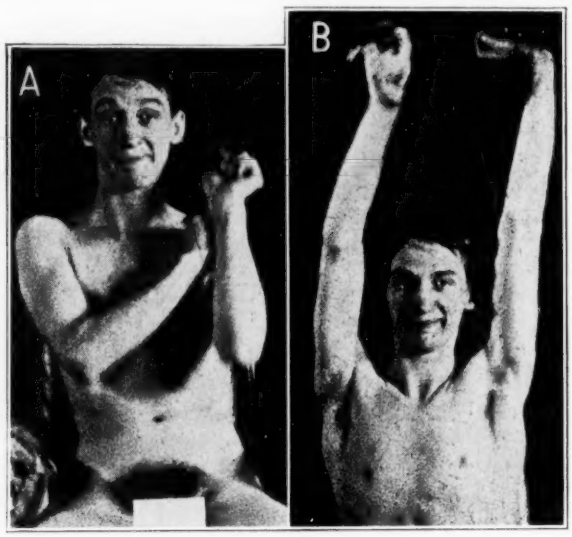

Fig. 3.—Patient during an attack induced by alcohol. *A*, flinging of the arms and grimacing. *B*, overpronation of the upstretched left arm, irregular flexion and spreading of the fingers and grimacing.

either with irregular flexion and extension of the fingers of one hand or with supination of one foot. Occasionally both the upper and the lower extremity on the same side were involved simultaneously, followed in a few seconds or a few minutes by involvement of the face, the body and the extremities of the opposite side. The initial movements of the fingers were succeeded by adduction and internal rotation of the arm at the shoulder, flexion of the arm at the elbow and wrist and flexion of the fingers at the metacarpophalangeal joint. The fingers were then slowly and irregularly extended, flexed and spread. Rather wild flinging movements occurred in the upper extremities, interfering with such skilled acts as removing his sock. In the lower extremities there was a tendency to equinovarus posturing of the feet. When he was lying down or sitting the legs were frequently extended, flexed and rotated externally in a wild flinging manner. The big toes were frequently dorsoflexed in a movement resembling the Babinski reaction. Furthermore, torsion spasm frequently appeared. There were marked choreoathetoid movements involving the facial muscles and producing grimaces. At times the neck was hyperextended and the eyes were rolled upward. Speech became slow, somewhat slurred and then impossible. Breathing became increased in rate and noisy, with clucking sounds and loud expiratory grunts.

Examination during an attack showed the patient to be conscious, mentally clear and oriented. All movements of the eyes were markedly restricted, but the pupils reacted satisfactorily. When he attempted to walk dancing movements occurred in the lower limbs, sometimes throwing him off balance. The upstretched arms showed overpronation. Between muscular contractions one had the impression of marked hypotonus. Purposeful voluntary movements were executed in a clumsy fashion characteristic of parakinesias, as seen in patients with Huntington's chorea. The deep reflexes were difficult to elicit, especially in the upper extremities. The abdominal reflexes were diminished. Because of the many movements of the toes and ankles it was difficult to examine for the Babinski toe reflex, but one had the feeling that there was no true Babinski toe reflex present.

The attack described represents one of the "large" variety. The "small" attack differed from it only in severity. The duration of the paroxysms varied from a few minutes to as long as four hours. They occurred at any time of day, irrespective of meals. Sleep was the only thing that relieved an attack.

On three occasions 90 cc. of whisky U. S. P. produced typical attacks. Otherwise the attacks could not be precipitated by any of the numerous methods attempted. Hyperventilation produced no untoward symptoms, but a Chvostek sign was present. Caffeine with sodium benzoate was administered. Hydration was also fruitless. He was given, at different times, 1,000 cc. of tap water in one hour, 1,000 cc. of tap water and 15 Gm. of sodium chloride in one hour, and 5,600 cc. of tap water and 3.4 cc. of pitressin in divided doses during twenty-eight hours. He was placed in a tub of cold water (60 F.) for one minute and five minutes later, in a tub of hot water (110 F.) for five minutes. He walked up and down fifteen flights of stairs, of nineteen steps each. Ninety per cent nitrogen and 10 per cent oxygen was inhaled for thirty minutes, 100 per cent oxygen for ten minutes, 100 per cent carbon dioxide for three minutes and 90 per cent oxygen and 10 per cent carbon dioxide for ten minutes. About three minutes after the last inhalation was completed he began to have a typical attack, which lasted for two hours. It was believed that no conclusion with respect to a cause and effect relation could be reached because of so many extraneous factors.

Scopolamine hydrobromide was the only drug which seemed to benefit him. He received 0.004 Gm. twice a day. The frequency, severity and duration of the attacks were greatly reduced. He had only four minor paroxysms in the first seventeen days after its administration was begun. Soluble phenobarbital had no effect. Benzedrine sulfate and potassium chloride were likewise without benefit. Although dilantin has never proved helpful in treatment of disturbances of the striopallidal system, it was given a trial. It increased the severity, frequency and duration of the attacks. Paraldehyde administered during an attack, on one occasion only, seemed to lessen the severity of the attack, and the paroxysm disappeared when the patient went to sleep about one-half hour later.

COMMENT

The purpose of this report is to present a new clinical syndrome without attempting at this time to describe the mechanism by which it is produced. The attacks are typically choreoathetoid, but at their height the similarity to those of Huntington's chorea is marked. Like disorders of the basal ganglia, the attacks ceased when the patient went to sleep; and they never appeared during sleep. The paroxysmal occurrence and the electroencephalographic findings suggest a resemblance to epilepsy, but hydration or hyperventilation failed to produce the attacks. None of the encephalographic features reported by Putnam in cases of athetosis and allied disorders were found. The atypical Kayser-Fleischer ring indicates a relation to lenticular disease. The low basal metabolic rate and the flat dextrose tolerance curve were considered to be independent of the presenting syndrome.

The patient's family history was carefully traced and checked. The transmissibility is apparently a non-sex-linked recessive hereditary characteristic; both males and females are affected, and the attacks have never appeared in the siblings of unaffected parents. Life expectancy in persons having attacks was not impaired. The patient's great-grandfather, in whom the attacks originated, reached the age of 87. One great-aunt and 1 great-uncle, both of whom had attacks, are still living. The former is 72 and the latter is 81.

Questionnaires were sent to the patient's kinsmen, who are scattered through the southern states, from South Carolina to Oklahoma. To date seven have been returned. These showed the nature and duration of the attacks to be identical with those of the patient. However, in 2 cases there was biting of the tongue. In all but 1 instance the attacks were less frequent than in the case studied. In all 7 the attacks were precipitated by alcohol. Other factors, in order of frequency, were coffee, tea, fatigue, tobacco, concentration, coca cola, exercise and hunger. Four of the relatives obtained relief by sleep; the other 3 knew no way to obtain relief. The onset was in infancy in each case.

Dilantin has proved to be ineffectual in the treatment of diseases of the striatal system and frequently has resulted in an increase of symptoms. The results of its administration in this case were therefore anticipated. The expected results were likewise obtained on giving benzedrine sulfate, which is effective in increasing motor and mental activity.

Scopolamine hydrobromide has been used to lessen tremor, to diminish muscular tone and to act as a cerebral sedative. It has been described as a depressant of the central nervous system, including the psychic and

motor centers, even the motor cells of the spinal cord. It also acts twice as strongly on the nerve terminations as atropine. Since scopolamine hydrobromide has such a widespread action on the nervous system, no conclusion was reached to explain the therapeutic effects obtained.

The fact that the attacks can be precipitated by alcohol suggests a release of the lower motor centers from cortical control. Alcohol produces cerebral depression which follows the reverse of the evolutionary order, the centers last developed being the first affected. How far the depression progresses in this case is speculative. At no time did the patient exhibit the commonly recognized signs of acute alcoholic poisoning, except for slight euphoria. However, the alcohol did release the inhibition which controls the effector mechanism of choreoathetosis, whether this mechanism is located in the cortex or in the corpus striatum. It is interesting in this connection that Klingman and Carlson of this clinic reported diminution or abolition of choreoathetoid movements following the intake of alcohol in relatively small amounts.

We wish to emphasize that this is a preliminary report and that the results of further observation of the patient and study of his family will be published at a later date.

SUMMARY

A case of a new clinical syndrome is reported, with detailed observations on a patient presenting this syndrome and a careful study of his family tree.

CHRONIC ENCEPHALITIS

Pathologic Report of a Case with Protracted Somnolence

RICHARD B. RICHTER, M.D., AND EUGENE F. TRAUT, M.D., CHICAGO

Several years ago one of us [1] recounted the clinical history of a patient who was of interest because of the extraordinarily long period of somnolence which she had suffered and which, in combination with other signs, had led to a diagnosis of chronic lethargic encephalitis. This patient has since died, and the following pathologic study is reported because the nature and distribution of the changes represent a somewhat unusual and not well known picture of chronic encephalitis and because of the light which the observations cast on the anatomic basis of pathologic sleep.

REPORT OF CASE

Clinical Summary.—In February 1932 Patricia Maguire, aged 26, after several days of progressive drowsiness, sank into five years of almost unbroken sleep. Within twenty-four hours of the onset of her illness there were paresis of the left third cranial nerve and slight narrowing of the right visual field. During the first two weeks sleep was interrupted only by active delirium. Fever appeared. The leukocyte count was 11,000 per cubic millimeter. The Kahn reaction of the blood was negative. The spinal fluid was clear, contained 8 lymphocytes per cubic millimeter and showed a slight increase of globulin and a normal amount of sugar; the Wassermann reaction was negative, and the Lange curve was 0000133320. The stupor deepened until she could not be roused. She emptied the bowels and bladder in the bed. Tube feeding was instituted and was continued for years. The neck was not stiff. Ankle clonus was present bilaterally. The Babinski sign was positive on both sides. Ptosis and external strabismus of the left eye, which had appeared early, soon disappeared. Right external strabismus developed and persisted. She had projectile vomiting and convulsive stiffenings of the whole body, including the neck. Within two weeks her whole body was rigid. The rigidity offered an even resistance, of the extrapyramidal type. The fever and convulsions subsided in about two weeks. Rigidity persisted although to a lesser degree. According to her mother, she would completely relax during the night's sleep, and often we found her relaxed during the day, apparently "asleep." A stimulus would awaken her with a start.

After the disappearance of the acute symptoms she began to move her arms and legs to change position. She would yawn as if extremely weary and fall back into a stupor, with eyes partly closed. During intervals of near wakefulness she would grimace, pulling one corner of her mouth upward and the other downward. The pupils remained small and equal and after a time did not respond to light but reacted in accommodation. The left leg would at times jerk rhythmically.

From the Department of Medicine of the University of Chicago; the Morton D. Hull Fund for Medical Research, and the Department of Medicine of Rush Medical College, University of Chicago.

1. Traut, E. F.: The Case of Patricia Maguire, J. A. M. A. **104**:1210 (April 6) 1935.

The pulse remained accelerated for years, and the oral temperature was frequently between 99 and 100 F. On a diet of egg, milk, butter, sugar, cod liver oil and brewers' yeast, fed by tube she gained weight so rapidly that the 3,000 calory ration had to be reduced. Except for slight elevation of the total protein content, the spinal fluid was normal.

Five months after the onset she was improved enough to smile. She could overcome the right external strabismus and follow a finger with both eyes coordinately. Throughout the course of the disease, except for the first three weeks and the last two days, she blinked her eyes defensively if a finger were suddenly thrust toward them. This proved her ability to see. Six months after the onset she would grasp her abdomen as if in pain about thirty minutes after eating. Shortly thereafter, on two occasions, she vomited a cupful of blood. These symptoms were assumed to be due to an acute peptic ulcer caused by a lesion of the interbrain. The symptoms disappeared when she was placed on a modified Sippy regimen. In addition to the rigidity, there developed a stare, and occasionally a fine tremor was present during rest. Drooling was so marked that inflammation of the cheek appeared. Pads had to be placed under her head to avoid soaking of the pillow. Her tolerance to dextrose, administered orally, was somewhat low. Lobar pneumonia developed, from which she recovered subsequent to the injection of types I and II combined antipneumococcus horse serum.

After one and a half years her general condition was good. Tests of the blood and urine gave normal results. She had almost constant coiling athetoid movements of the arms. There were periods, varying from one-half to one hour, when she was awake and alert. She learned to call for the bed pan by grunting. She answered various questions by assenting or objecting to the number of raised fingers. One or both pupils would suddenly dilate and then, as suddenly and without apparent cause, contract. Rapid nystagmoid side to side jerking of the eyes developed. The abdominal reflexes were absent. Usually, ankle clonus could be elicited bilaterally. Contractures of both great toes developed as a result of constant extension. She snored at night. She could turn over if placed on her face. She resisted with great strength and agility such unpleasant procedures as catheterization or spinal puncture. She lay characteristically on her back, with her arms flexed to the maximum at the elbows and wrists. The fingers were flexed at the junction of the second and third phalanges, and the thumbs were flexed and strongly adducted. Her head was drawn to the right. Her mouth was distorted to a leer. Her eyes were closed tightly. Her legs were extended and adducted, with the great toes in marked extension. The other toes were flexed. The trunk was straight. The hands made athetoid movements. During the day she grunted in a singsong way, in an alto pitch. Her body and extremities were held rigidly, but she could relax at will. She resisted any attempt to change her position and expressed her displeasure by louder and more frequent grunts. She might open her eyes and view visitors without turning her head or might pay no attention to them, even when requested. She responded to pinpricks anywhere on her body by wincing and moving her arms and legs in defensive and escape attempts. Food placed in her mouth would not be chewed or swallowed. When she was raised to the sitting position her head would fall forward on her chest, choking her, and her shoulders would slump toward her knees.

In August 1937 a fluctuating tumor resembling a football was noted in the left side of the abdomen. It was attached in the pelvis. Phlebitis developed in the left leg. After swellings due to distention of the bladder, uterus, colon and kidney pelvis were ruled out, the tumor was taken to be a cyst of the left ovary. While operative removal was being discussed the tumor suddenly disappeared.

On reappearance of the tumor the patient was removed to the Presbyterian Hospital. Pneumonia developed and she died on Sept. 28, 1937.

During the five years of her illness many methods of treatment were employed, which at best may be credited with prolonging life.

General Autopsy Observations.—The essential observations at autopsy, other than those in the brain, were confluent bronchopneumonia in both lungs, a large papillary cystadenoma of the left ovary, filled with blood, and an organizing clot in the left external iliac vein.

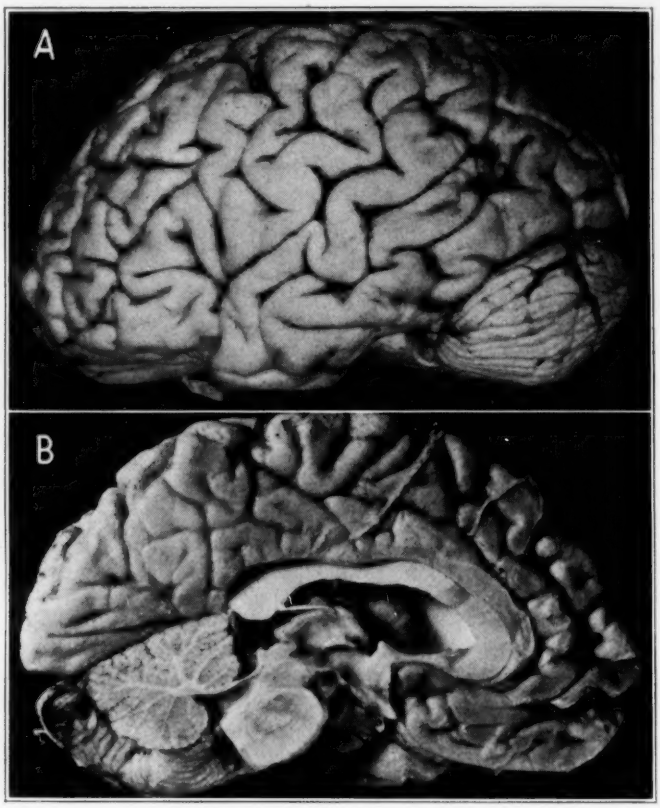

Fig. 1.—Left cerebral hemisphere, showing (*A*) moderate generalized convolutional atrophy and (*B*) enlargement of the ventricular system and extreme thinning of the floor of the third ventricle.

Gross Cerebral Changes.—The formaldehyde-hardened brain weighed 1,140 Gm. The leptomeninges of the convexity and the base were everywhere thin and translucent and were nowhere adherent to the surface of the brain. The arteries of the base, comprising and arising from the circle of Willis, were thin walled, with smooth linings, and were free from thrombi.

The external appearance of the cerebellum and brain stem, together with the cranial nerves, was normal in every respect. The convolutional pattern of the

cerebral hemispheres was likewise normal. There was slight to moderate convolutional atrophy, generalized over the anterior half of the brain on both sides and more pronounced over the frontal lobes (fig. 1*A*). Sagittal section of the brain in the midline revealed extensive and symmetric dilatation of the lateral ventricles and of the third ventricle (fig. 1*B*). The aqueduct of Sylvius was open and of at least normal size, and there was no obstruction of the ventricular channels elsewhere. The enlargement of the lateral ventricles was attributable to atrophy of the head of the caudate nucleus, as well as to atrophy of the surrounding hemispheres. The third ventricle was 31 mm. in length, 13 mm. in depth and 14 mm. in its greatest width. This great enlargement had occurred at the expense of the gray matter of the diencephalon, which had undergone atrophy to the extent that the massa intermedia was a flat ribbon of tissue 6 mm. wide, 1 mm. thick and 14 mm. long. The floor of the third ventricle was thin as paper. The mamillary bodies appeared of normal size on ventral view, but were less than 1 mm. thick. Except for the atrophy of the structures noted, the cut surfaces of both hemispheres appeared normal on frontal section, except in the region of the lenticular nucleus, the ventral border of which had a cribriform appearance, extending into the globus pallidus. This change was about the same in degree and location on the two sides. Cross sections through the brain stem likewise showed no gross abnormalities. It was especially noteworthy that there was no gross atrophy or depigmentation of the substantia nigra.

Microscopic Cerebral Changes.—Cortex and Subcortical White Matter: Sections taken from representative regions of the frontal, temporal, parietal and occipital lobes and of the central area of each side of the brain on the whole showed relatively little alteration of the cortex when stained by the Nissl method (fig. 2*A*). Mild to moderate nonspecific changes in scattered ganglion cells and occasional small areas of cellular clearing were present, together with some diffuse increase of glia. In places there was considerable increase of satellite glia around ganglion cells in the deepest layers of the cortex, but this was not prominent. The cortex was everywhere reduced in width. The greatest changes were seen in the precentral and postcentral convolutions, especially on the left side. Here the width of the cortex of the precentral gyrus was 1.5 to 2 mm., and that of the postcentral gyrus 1 to 1.5 mm. The cortical lamination, while discernible, was much obscured, partly through diffuse outfall of cells, partly through disorientation of those remaining. Many of the cells present, including the Betz cells, showed such changes as rounding, defective staining of the tigroid substance and eccentricity of nuclei.

The most obvious alteration was the striking increase of glia nuclei, which occurred diffusely everywhere in the subcortical white matter. In many places there was also evidence of progressive changes in glia cells in the form of swollen cytoplasm and hyperchromatic nuclei. In Pal-Weigert preparations of the aforementioned regions there were everywhere diffuse paleness and thinning of myelin, without any patchy or focal demyelination (fig. 2*B*). The radiary fibers in the cortex were well preserved, but there was some reduction of the tangential and supraradiary fibers and of those of the zone of Baillarger. Holzer stains of cortical and subcortical areas showed no fibrous gliosis.

Basal Nuclei: While the alterations in the thalamus were relatively less than those of the other basal ganglia, they were nevertheless distinct. Parenchymatous changes were limited to degeneration of single ganglion cells, sometimes marked and accompanied by increase of satellite glia. A diffuse increase of glia nuclei was evident, and in places there were also focal clusters of glia cells. With the

Holzer stain there was light, patchy fibrous gliosis. There were perivascular infiltrations of lymphocytes and plasma cells, but these were few and not intense. They were mostly at the borders of the thalamus, near the surrounding white matter. In one region an interstitial infiltration of plasma cells was seen (fig. 3 *A*).

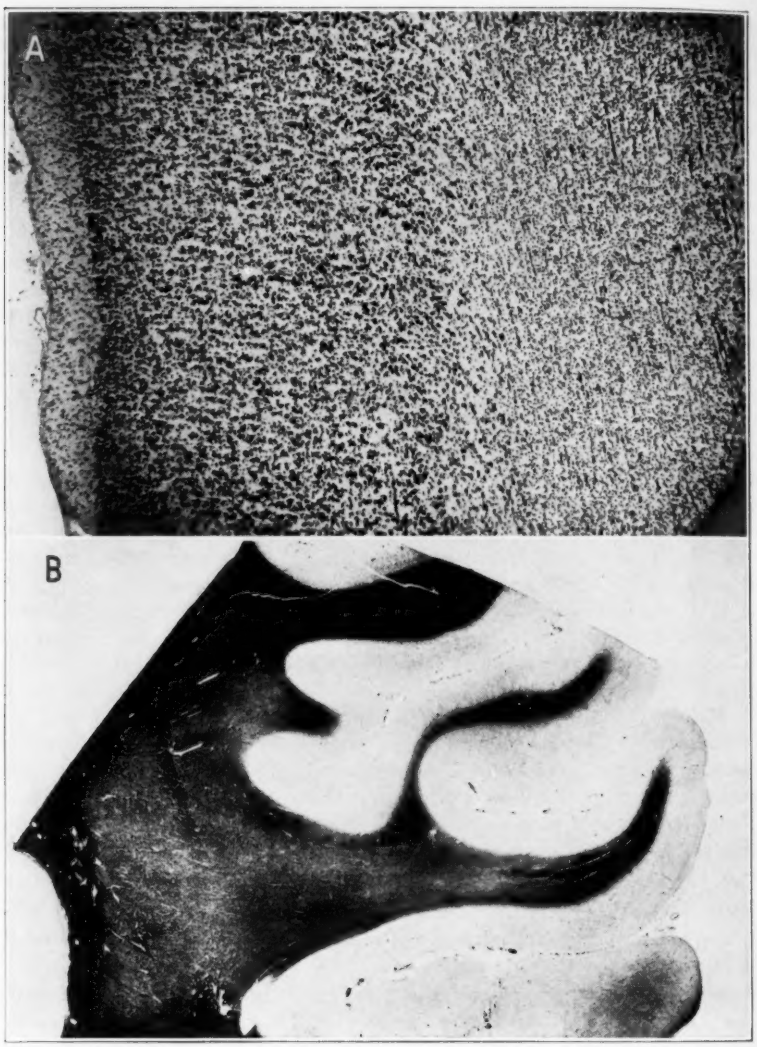

Fig. 2.—*A*, left superior frontal gyrus, showing normal cortical architecture and gliosis of the white matter. Nissl stain. *B*, right centrum semiovale, showing diffuse paling of the myelin. Pal-Weigert stain.

The situation in the striatum was like that in the thalamus. In both the caudate nucleus and the putamen there were nonspecific degenerative changes of isolated neurons, mostly of the large cell elements, consisting of partial to com-

plete dissolution of tigroid substance, marked displacement of nuclei and occasionally neuronophagia. More anteriorly there was some outfall of these cells. Several circumscribed, round, pale, acellular areas were present in the putamen.

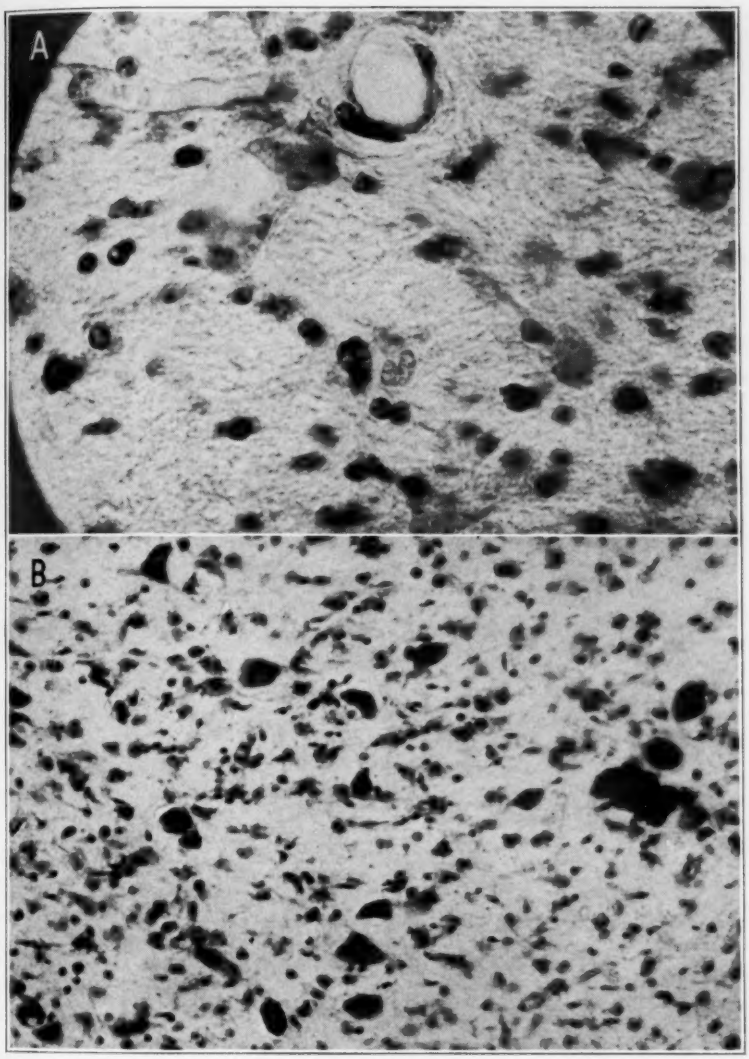

Fig. 3.—*A*, gliosis and interstitial infiltration of plasma cells in the thalamus. Nissl stain. *B*, globus pallidus, showing degeneration of neurons and marked gliosis. Nissl stain.

Within these devastated regions were a few pyknotic ganglion and glia cells. There was a patchy increase of glia nuclei throughout the striatum. A number of the glia cells contained blue or green-black granular material in Nissl prepa-

rations. Holzer stains revealed no fibrous gliosis except around some of the larger vessels and within the radiations of the internuncial fiber tracts. A number of the vessels were infiltrated, mostly by macrophages containing dark green pigment and lymphocytes, but occasional plasma cells were also present.

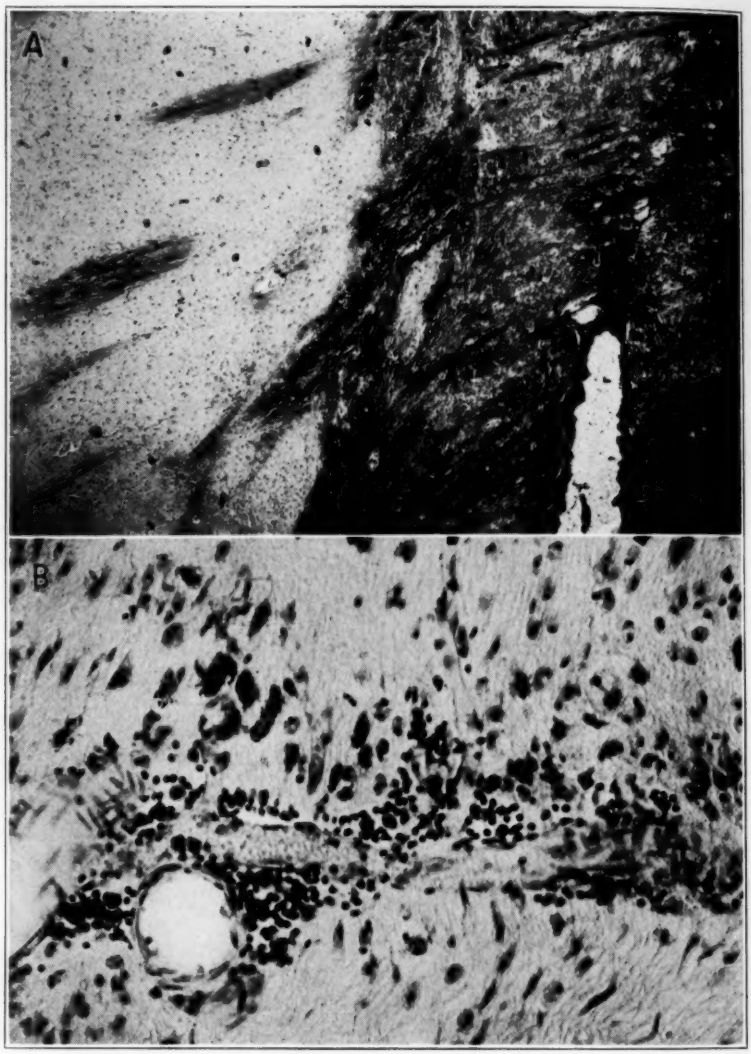

Fig. 4.—*A*, lenticular nucleus. Note the dense fibrous gliosis in the globus pallidus on the right, which leaves off abruptly at the putamen. Holzer stain. *B*, perivascular infiltration of lymphocytes and plasma cells in the globus pallidus. Nissl stain.

The globus pallidus was the site of marked destruction. The ganglion cells were greatly reduced in number, and all those remaining showed advanced retrogressive changes. They were rounded and completely devoid of Nissl substance,

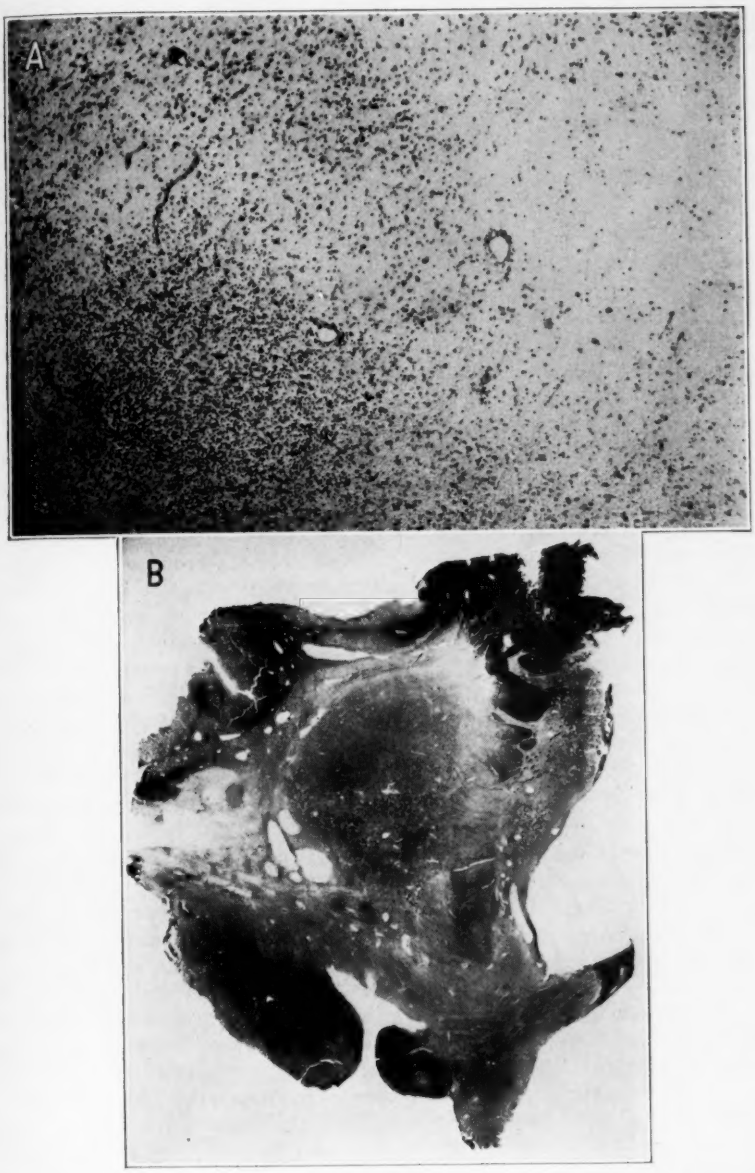

Fig. 5.—*A*, gliosis and perivascular infiltrations in the region of the external capsule, with status spongiosus on the right. Nissl stain. *B*, diffuse demyelination in and around the lenticular nucleus, including the internal capsule. Spielmeyer myelin stain.

and the cell bodies contained large amounts of purplish yellow pigment (fig. 3*B*). In addition, there was a marked glial reaction throughout the nucleus, with giant, lobulated and rod-shaped glia cells in enormous numbers. Many of the glia cells were packed with pigment granules, some of them staining dark blue in Nissi preparations and some a dirty brown, as if derived from blood. When stained by the Gömöri [2] method these glial inclusions gave a positive reaction for iron. Holzer stains revealed a dense glial scar occupying the whole extent of the globus pallidus (fig. 4*A*). There were a number of dilated, tortuous vessels within the globus pallidus. About these and other vessels within the nucleus there were often heavy infiltrations of macrophages, lymphocytes and plasma cells (fig. 4*B*).

In the white matter surrounding the basal ganglia, the subcortical white matter of the insula, the external capsule, the internal capsule and the ansa lenticularis there were extensive and pronounced changes. In Nissl preparations there was a tremendous increase of glia nuclei in all these regions. Most of the glia cells were normal, but in many places they exhibited hyperplastic changes. In the region lateral to the putamen and beneath the cortex of the insula there were pale, acellular fields containing a few dark, shrunken cells. In the same area there were also regions of status spongiosus, and the perivascular spaces of many of the vessels were enormously dilated, producing a cribriform state (fig. 5*A*). A few small foci were observed within the internal capsule which were crowded with hyperplastic astrocytes, free plasma cells and scavenger cells resembling gitter cells. With the Holzer stain there was dense fibrous gliosis in the corresponding regions, less thick in the internal capsule than elsewhere. For the most part, this formed an isomorphous glial scar, but in some places, especially in the region of the external capsule, it was extremely disorderly. Throughout the area in question there were numerous perivascular infiltrations of moderate intensity composed of lymphocytes, plasma cells and macrophages. These were especially striking at the borders of the spongy areas; here were also a few gitter cells in the perivascular spaces, but no foci of softening were encountered in the white matter. Myelin stains of the region of the basal ganglia revealed diffuse and profound paling of the caudate and lenticular nuclei and the surrounding white matter, including the internal capsule and ansa lenticularis (fig. 5*B*).

Hypothalamus: In spite of the marked wasting of the region grossly, the nuclei of the anterior part of the hypothalamus were surprisingly well preserved (fig. 6*A*). Isolated ganglion cells of the supraoptic and filiform nuclei and of the nucleus basalis presented mild to moderate retrogressive changes, but on the whole they were in good condition. The nucleus mamilloinfundibularis was nearly normal. There were somewhat greater changes in the nuclei tuberis, with an appreciable outfall of cells. There was a striking increase of glia in all these nuclei. In the posterior part of the hypothalamus, however, there was extreme destruction. The posterior hypothalamic nuclei were not found, and the nuclei of the mamillary bodies had completely disappeared (fig. 6*B*). Holzer stains revealed a moderately dense feltwork of glia fibers in the nucleus supraopticus and nucleus basalis and dense glial sclerosis occupying the optic tract, fornix, field of Forel and lateral wall of the third ventricle in its superior portion (fig. 6*C*). The lower part of the lateral wall and the floor of the third ventricle did not present such a scar but had undergone only atrophy, without reactive fibrous gliosis. The corpus Luysi showed the same relatively insignificant degen-

2. Dr. George Gömöri made these preparations.

erative changes in isolated ganglion cells as were seen in the thalamus, but with rather less glial proliferation. The entire hypothalamic region was practically without myelin (fig. 5*B*). The optic tract and fornix appeared much paler than normal with the Spielmeyer stain for myelin. All the foregoing changes were essentially similar on the two sides of the brain.

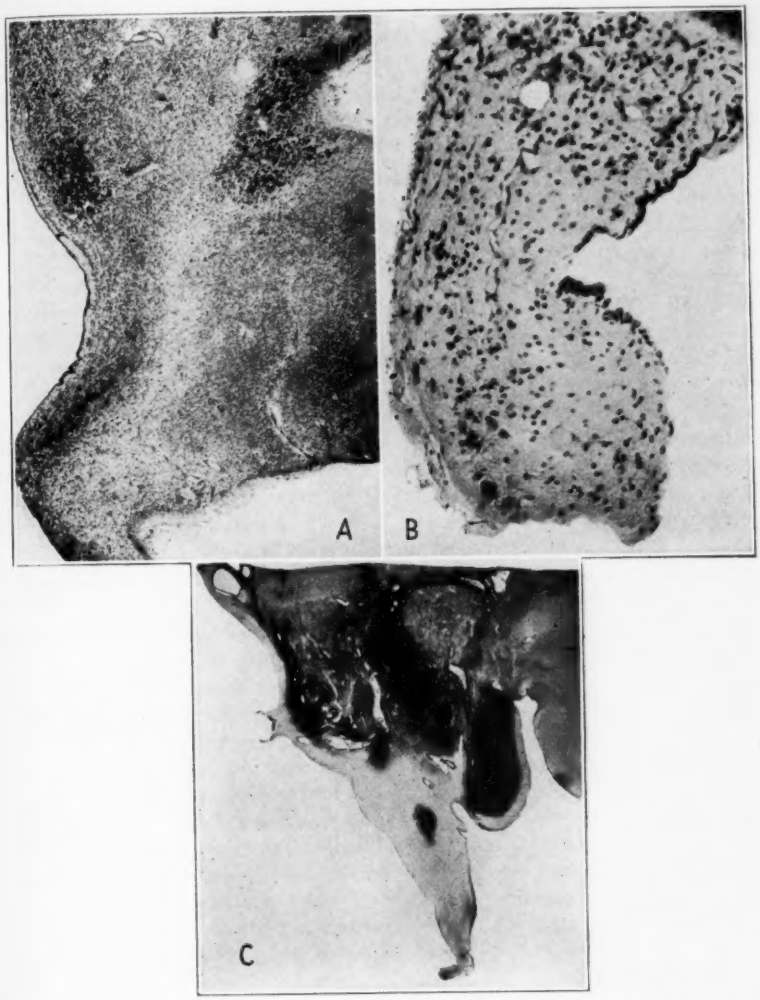

Fig. 6.—*A*, relatively well preserved supraoptic and filiform nuclei and outfall of cells in the tuberal nuclei. Note diffuse gliosis of the entire hypothalamic region. Nissl stain. *B*, region of the mamillary body, showing extreme atrophy and total absence of ganglion cells in the mamillary nuclei. Nissl stain. *C*, posterior portion of the hypothalamus, showing heavy glial scar in the optic tract, internal capsule, ansa lenticularis, fornix and paraventricular region. Holzer stain.

Brain Stem: In the midbrain the nuclei of the third and fourth cranial nerves were well preserved. A number of the cells of the reticular formation of the

tegmentum were swollen and had eccentric nuclei. Throughout the nucleus ruber were isolated cells which showed mild to moderate degenerative changes and, in addition, regions within the nucleus where there had been an extensive outfall of cells, accompanied by gliosis. In the rostral portion of the substantia nigra there was moderately severe damage, with outfall of some cells and atrophy, distortion and depigmentation of others. Scattering of pigment, which either lay free or was taken up by the glia cells, was also noted to some degree. There was considerable proliferation of glia within the nucleus, with formation of Hortega cells. Within and near the substantia nigra at this level the perivascular spaces of many of the vessels were greatly dilated and empty, and where such vessels lay close together an état criblé resulted. At the level of the peduncle, however, the outfall of cells in the substantia nigra was not great, and the appearance of the nucleus on the whole was more nearly normal. There was extensive patchy gliosis of the tegmentum, with hyperplastic astrocytes and Hortega cells. Along the medial edge of the tegmentum and in the caudal portion of the inferior colliculus a status spongiosus had developed. Intense fibrous gliosis was present both in the tegmentum of the midbrain and in the pes pedunculi (fig. 7*A*). This scar involved all the principal nuclei—those of the oculomotor nerve, the substantia nigra, the red nucleus and the superior colliculus. There was marked fading of myelin throughout this region. The tegmentum, including the red nucleus and its capsule, was almost completely demyelinated. The lateral and medial lemnisci, the posterior longitudinal bundle, the brachium of the inferior colliculus and the pes pedunculi were all involved. Numerous perivascular infiltrations, mostly of lymphocytes with an admixture of plasma cells and large scavenger cells, were present in both the basilar portion and the tegmentum of the midbrain, but were more numerous in the former. They were observed within the oculomotor nucleus, the red nucleus and the substantia nigra (fig. 7*B*).

In the pons the ganglion cells of the locus caeruleus, the nucleus masticatorius and the pontile nuclei were relatively intact, although in all these locations individual cells were degenerated. Retrogressive changes were more common in the cells of the central gray substance and the dorsal nucleus of the raphe. A diffuse increase of glia nuclei was present in both the tegmentum and the basilar portion of the pons. This was much greater in the rostral than in the caudal part. Similarly, the glial fibrosis was much heavier in the rostral portion. Here the tegmentum was diffusely involved, with extension into the periventricular gray matter and the nucleus of the fourth cranial nerve. The sclerosis was densest in the long fiber tracts, the brachium conjunctivum and its decussation and the medial lemniscus. In the pars basalis there was an isomorphic glial scar in the transverse pontile and descending pyramidal bundles, which extended into the pontile nuclei. This was more dense laterally. At the more caudal levels the glial sclerosis fell off appreciably in degree and extent and was practically limited to structures in the tegmentum, the gray matter of the floor of the fourth ventricle, the brachium conjunctivum and the medial lemniscus. There was a similar sharp difference in the degree of involvement of the rostral and the caudal level of the pons in the myelin sheath preparations. At the rostral level there were virtually complete absence of myelin in the tegmentum, including the brachium conjunctivum and its decussation, and marked fading of transverse pontile fibers in the pars basalis (fig. 8*A*). Corresponding with the gliosis, the myelin damage was greater in the lateral portion. The descending pyramidal fasciculi at this level were even paler than the transverse pontile fibers. In the caudal portion of the pons, on the other hand, the myelin pattern was much better preserved. The transverse pontile fibers and brachium pontis were well stained. The most evident and constant

myelin degeneration was in the pyramidal fasciculus. Scattered perivascular infiltrations similar to those seen elsewhere were encountered, but were less numerous and striking than in the midbrain.

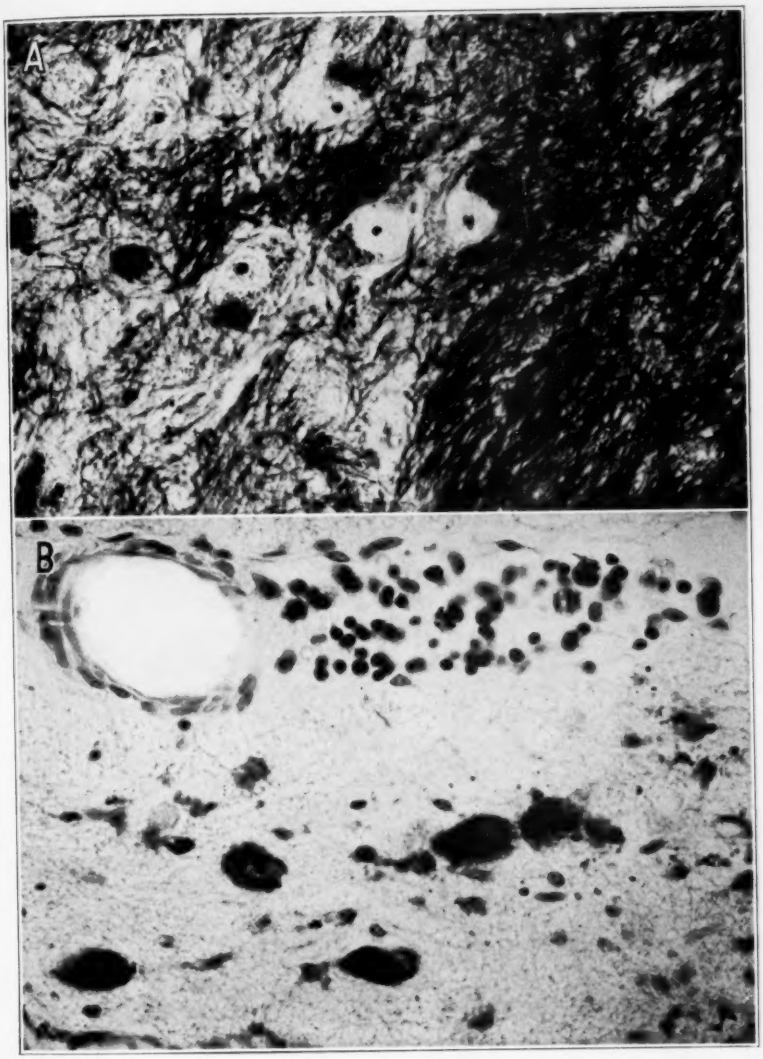

Fig. 7.—*A*, dense glial scar of the pes pedunculi (right), with glial feltwork extending into the substantia nigra on the left. Holzer stain. *B*, perivascular infiltration of lymphocytes, plasma cells and macrophages in the substantia nigra. Nissl stain.

In the medulla the alterations in ganglion cells, gliosis, demyelination and perivascular exudates were comparatively slight. There was some paleness of the pyramids with the myelin stains, but no glial sclerosis. The most outstanding

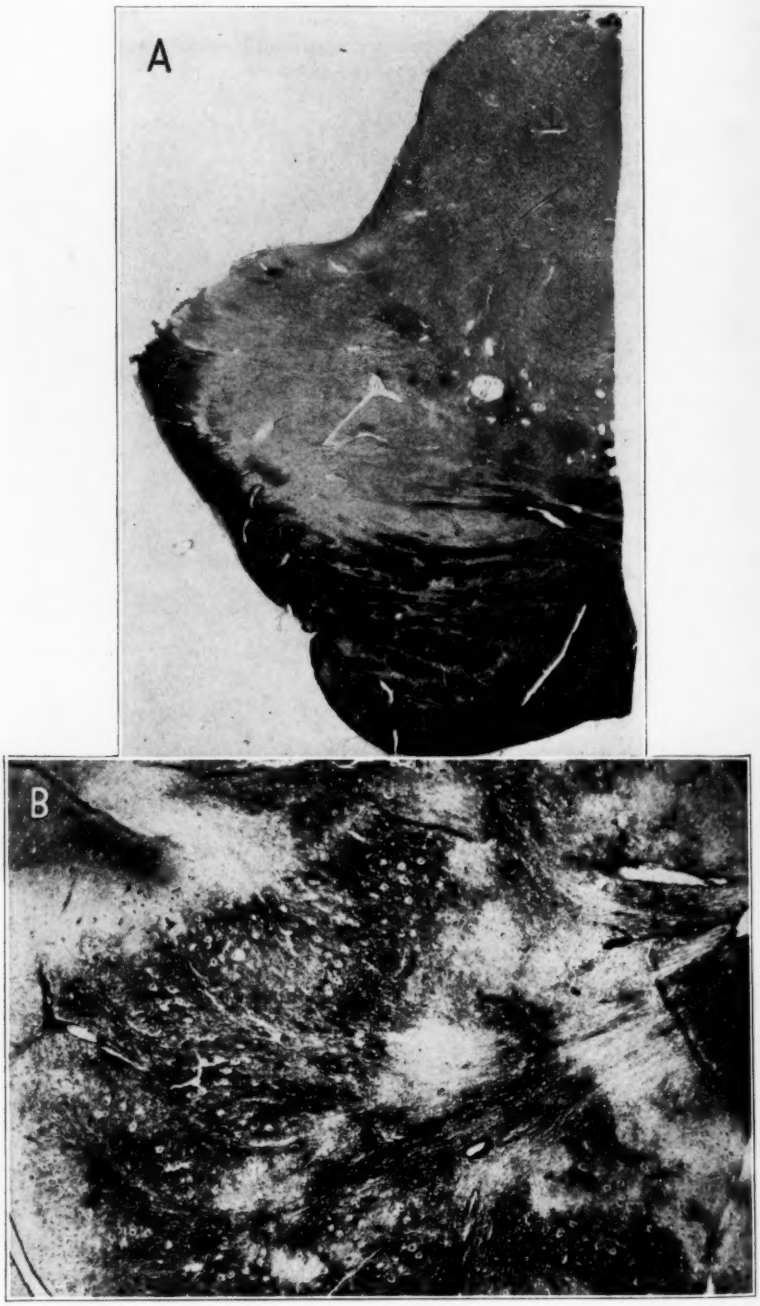

Fig. 8.—*A*, upper portion of the pons, showing extensive demyelination of the entire tegmentum and the dorsolateral portion of the pars basalis. Spielmeyer myelin stain. *B*, fibrous gliosis of the inferior olives. Holzer stain.

alteration in this part of the brain was a dense glial scar in the inferior olives (fig. 8*B*). This did not extend into the olivocerebellar tracts.

Cerebellum: The changes in the cerebellum were also relatively slight and were limited to nonspecific degenerative changes in isolated cells of the dentate

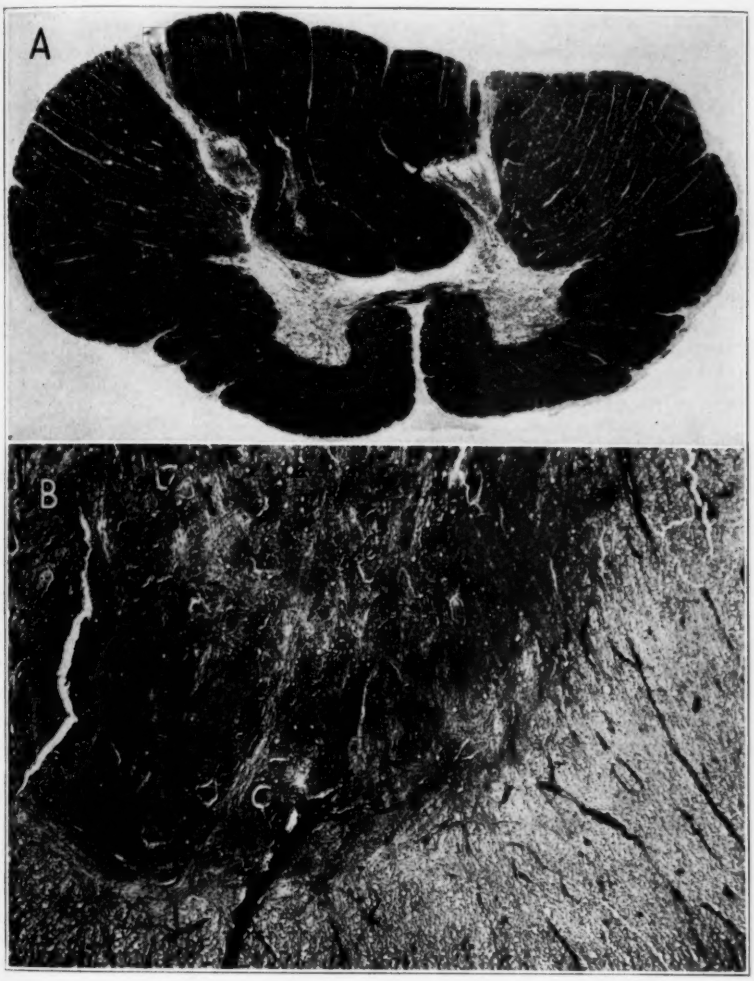

Fig. 9.—Cervical portion of the cord, showing (*A*) demyelination of the anterior horns and (*B*) fibrous gliosis of the anterior horn. Holzer stain.

nucleus, some thinning of the granular layer, diffuse increase of glia nuclei in the white matter and a few perivascular infiltrations, also in the white matter.

Spinal Cord: In Nissl preparations there was marked atrophy of the anterior horns at the cervical level, with reduction of the number of cells and atrophic changes in those remaining. Demyelination of the white columns was not apparent at any level with the Pal-Weigert stains, but the myelin network of the anterior and

posterior horns in both the cervical and the dorsal portion of the cord was broken up and disorganized, with typical degenerative changes in the individual fibers (fig. 9 *A*). At these levels, in Holzer preparations there was heteromorphic fibrous gliosis of the anterior horns, but not of the posterior (fig. 9 *B*). In addition, there was some increase of glia fibers everywhere in the white matter. This was not dense, but appeared in the form of a network, which was orderly and followed the arrangement of the normal glia reticulum. The lumbar portion of the cord appeared normal with Nissl and Pal-Weigert stains, but here also there were some fibrous gliosis in the anterior horns and a number of foci of glial scarring in the white matter, mostly in the posterior columns but also in the lateral.

Neurofibrils: Bielschowsky preparations were made of the basal nuclei, the midbrain and the pons. Everywhere the staining of neurofibrillar structures was defective in the ganglion cells of the principal nuclear groups. Either there was absence of any structures impregnated with silver in the cytoplasm of the cells or there were deposits of a granular argentophilic substance, dispersed or compact. In no case were there seen any formations resembling the Alzheimer fibrillary change.

Meninges: For the most part the meninges were normal, but here and there were localized regions of fibroblastic hyperplasia or round cell infiltration or both. These were observed in the pia-arachnoid covering the hemispheres and in that of the brain stem.

Pituitary Gland: The structure of the anterior and posterior lobes of the pituitary appeared normal in hematoxylin-eosin, phosphotungstic acid hematoxylin and Foot's reticulum preparations.

COMMENT

The character of the changes present in this brain is essentially that observed in all cases of chronic epidemic encephalitis of the von Economo type, namely, focal or widespread destruction of the cell bodies of neurons, with reactive fibrous gliosis, associated with more or less inflammatory cellular reaction in the perivascular spaces of the regions involved. The distribution of the changes in the present case, however, is in marked contrast to the stereotyped picture in cases of chronic epidemic encephalitis, now so often reported in the literature, in which the destruction is virtually limited to the substantia nigra. It would appear that in the present case a chronic destructive inflammatory process had continued not only in the tegmentum of the midbrain but in all the gray matter, which was preferentially attacked in the acute phase of the disease, including the periventricular gray matter of the third ventricle, the periaqueductal gray matter, the tegmentum of the midbrain and pons, the globus pallidus, the anterior gray matter of the cord and, to a slighter degree, the corpus striatum and the thalamus. As in the distribution of the acute lesions, the cerebral cortex and the cerebellum were little affected. There is much more involvement of the white matter than is ordinarily seen. Because of the diffuseness of these changes and the isomorphic character of the glial scar in the white matter, it is our belief that the greatest part of the damage is secondary to the extensive destruction of the nuclear masses. But this is not exclusively the case, since some truly inflammatory foci were encountered in the white matter, such as the small lesion described in the internal capsule.

Cases which resemble this pathologically in one or more respects are common in the literature, as may be seen from the monographs of Stern,[3] Wimmer [4] and von Economo,[5] but seldom is the destruction so extensive, particularly that in the hypothalamus. Most notable here is the association of an unusual symptom complex with an extraordinary sort of damage to the brain. It would seem at first unjustifiable to attempt any correlation of the exaggerated somnolence with the localization of the destruction in a brain in which the changes are so widespread. Yet when this damage is considered against the background of what is now known of the pathologic changes of hypersomnia, we believe that they have at least corroborative meaning. Ever since Mauthner,[6] with Jacksonian insight, postulated that the gray matter about the third ventricle and aqueduct was the critical locus for the production of pathologic somnolence, isolated observations have been made which indicate that such is indeed the case. We wish not to review the evidence *in toto* here but only to refer briefly to the more convincing reports. Of the group in which the condition was caused by tumors, the much quoted case of Fulton and Bailey [7] seems the most valid. These authors described the case of a woman aged 28 who had suffered from polyuria, adiposity and amenorrhea for six years and from narcolepsy-like drowsiness for five years. At autopsy there was little, if any, sign of increased intracranial tension, but a fairly well circumscribed tumor (perithelial sarcoma of leptomeningeal origin) was observed to have invaded the entire tuberal and infundibular regions and the mamillary bodies. Pette [8] reported an instance of a man aged 38 with bilateral oculomotor palsy and right hemiparesis, who presented marked somnolence over a period of three months. The pathologic description is somewhat inexact, but a sharply circumscribed destructive lesion was seen to occupy the floor of the third ventricle and the periaqueductal gray matter. A less well delimited lesion, but one which implicated the same area, has been recorded by Lucksch [9] in a patient with bacterial endocarditis who was in a prolonged sleep for two weeks. At autopsy a localized abscess was disclosed which had destroyed the periventricular gray matter of the posterior part of the third ventricle and the periaqueductal gray matter of the anterior part

3. Stern, F.: Die epidemische Encephalitis, Berlin, Julius Springer, 1928.

4. Wimmer, A.: Chronic Epidemic Encephalitis, London, William Heinemann, Ltd., 1924.

5. von Economo, C.: Encephalitis Lethargica: Its Sequelae and Treatment, translated and adapted by K. O. Newman, New York, Oxford University Press, 1931.

6. Mauthner, L.: Zur Pathologie und Physiologie des Schlafes, Wien. klin. Wchnschr. **3**:445, 1890.

7. Fulton, J., and Bailey, P.: Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**: 145 and 261, 1929.

8. Pette, H.: Die epidemische Encephalitis in ihren Folgezustanden, Deutsche Ztschr. f. Nervenh. **76**:1, 1923.

9. Lucksch, F.: Ueber das Schlafzentrum, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:83, 1924.

of the aqueduct. The medial nucleus of the thalamus was also partly destroyed, especially on the left, as well as the left anterior colliculus. The floor of the third ventricle, including the mamillary bodies, was not affected. On comparing this case with Pette's, Lucksch found the common denominator to be the damage to the periventricular and periaqueductal gray matter; he therefore selected this as the significant locus of injury in pathologic sleep. Recently Globus [10] reported 2 cases in which the patients were deeply somnolent for six and twelve days, respectively. In each the lesions were extensive, but there was symmetric bilateral softening which involved the thalamus and extended downward into the area in question, the hypothalamus, as far back as the mesencephalic tegmentum.

Long ago DuBois [11] stated that he had induced abnormal sleep in marmots by the production of small destructive lesions in the region of the floor of the third ventricle. More recently Ranson [12] has given the same precision to this aspect of hypothalamic localization as he has to so many others, by the use of the Horsley-Clarke instrument. Eleven monkeys of a large series with lesions in the hypothalamus showed enduring somnolence up to thirty or forty days. From a detailed study of the lesions in animals which did and did not exhibit this symptom the conclusion was drawn that the lesion responsible lies in the posterolateral part of the hypothalamus and that destruction of the lateral hypothalamic nuclei is more important for the production of somnolence than destruction of the mamillary bodies and the mamillothalamic tract. One of us (R. R.) was able to duplicate these results in 2 rhesus monkeys by discrete lesions strictly confined to the posterior part of the hypothalamus. Because of failure to combat the effect of the associated hypothermia, however, the animals survived only five and seven days. During the entire postoperative period in both cases there were profound inertia and almost continuous sleep, from which the animals could be roused by relatively mild stimulation.

Von Economo and others, on the basis of the localization of the lesions in the lethargic-ophthalmoplegic form of acute epidemic encephalitis, have long held that destruction of the gray matter about the anterior end of the aqueduct and posterior part of the hypothalamus was the anatomic basis of the hypersomnia in this disease. Hitherto, there has been no impressive support for this idea from the observations in cases of the chronic form. Eaves and Croll [13] indicated that they found some such correlation in their study of 10 cases of chronic encephalitis, but the lethargic symptoms were so indefinite and the pathologic descriptions so sketchy that their statement is scarcely convincing.

10. Globus, J.: Probable Topographic Relations of the Sleep Regulating Center, Arch. Neurol. & Psychiat. **43**:125 (Jan.) 1940.

11. DuBois, R.: Le centre du sommeil, Compt. rend. Soc. de biol. **3**:2291, 1901.

12. Ranson, S. W.: Somnolence Caused by Hypothalamic Lesions in the Monkey, Arch. Neurol. & Psychiat. **41**:1 (Jan.) 1939.

13. Eaves, E. C., and Croll, M. M.: The Pituitary and Hypothalamic Region in Chronic Epidemic Encephalitis, Brain **53**:56, 1930.

In our case hypersomnia was the outstanding symptom, hypothalamic destruction the outstanding lesion. In the light of the considerations outlined, the inference seems justified that the two are directly related. Furthermore, the localization of the lesion responsible for pathologic sleep was more sharply delimited in this case than in most human material previously reported on, as the anterior portion of the hypothalamus was relatively spared. Not only was this sparing apparent anatomically, but there is also reason to believe that the anterior hypothalamic nuclei were relatively intact functionally, since symptoms known to follow their destruction, notably, obesity and polyuria, were lacking in this patient. The observations here are in complete accord with the experimental results of Ranson, with the interesting exception that no obvious disturbance of temperature control, such as was invariably present in monkeys with lesions in this location, was ever observed in our patient.

It may be objected that the profound disturbance of consciousness presented by this patient was not, properly, pathologic sleep, since in the earlier part of the illness it lacked the reversible quality of physiologic sleep. On the other hand, the state was not coma in the ordinary sense of the term. It resembled precisely that peculiar trancelike condition which neurosurgeons not infrequently encounter in patients after operations in the neighborhood of the third ventricle and midbrain. With time the depth of the sopor lightens, as in our case, so that by stimulation the patient can be roused to an awareness of and some degree of response to his surroundings. It is our belief that these states of prolonged and unbreakable sleep differ only in degree from the interruptible forms of hypersomnia and depend on more extensive damage to the structures of the posterior hypothalamus.

The material at hand is not suitable, either clinically or anatomically, for elucidation of the old and still open question of localization with reference to encephalitic parkinsonism. It is to be noted, however, that both regions of the brain commonly alluded to as the sites probably responsible for parkinsonian symptoms, the substantia nigra and the globus pallidus, presented inflammatory activity and neuronal damage. The substantia nigra was less severely injured than is usual in encephalitic parkinsonism; the globus pallidus much more so. Under these pathologic circumstances the only parkinsonian symptom ever observed was generalized plastic rigidity. This may be taken to favor the opinion expressed by Környey [14] and others that the rigid component of the syndrome is attributable to damage of the pallidum. But the complexity of the pathologic changes does not allow much weight to be given to this interpretation.

Finally, we wish to comment, with reference to the changes in this brain, on the probable nature of chronic encephalitis. In recent years there has been a growing tendency among many authors to adopt the viewpoint of Jakob that the disease is a progressive process, set off by the original acute infection, but not in itself inflammatory. We agree that in the usual case of chronic encephalitis it may be impossible to judge whether the slight perivascular infiltrations encountered represent a true inflammatory disease. But we believe that in this material

14. Környey, S.: Zur Histopathologie der Späterkrankungen der Encephalitis epidemica, Arch. f. Psychiat. **92**:372, 1930.

the sum of the numerous and intense perivascular exudates, the leptomeningeal infiltrations and the occasional interstitial infiltrations of inflammatory elements can mean only a continuing chronic infection.

CONCLUSIONS

An unusual example of chronic encephalitis of the von Economo type is reported. In our opinion the observations lend support to the following propositions:

1. Damage to the posterior part of the hypothalamus is the lesion responsible for the production of pathologic sleep in human beings as well as in experimental animals.

2. Chronic epidemic encephalitis is a persisting inflammatory disease.

DIABETES INSIPIDUS

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AND SAMUEL LIEBOWITZ, M.D., NEW YORK

While the literature concerning diabetes insipidus has become voluminous and the number of known cases of the disease in man seems to be reasonably large, there still remains a paucity of case reports in which histologic studies of the hypothalamus have been made with the use of serial sections. Fink,[1] in 1928, collected from the literature 107 records of necropsies in cases of diabetes insipidus, in 37 of which there was a lesion involving the hypophysis, in 40 no lesion of that structure but some disturbance of the hypothalamus and in the remainder a wide variety of intracranial changes. In all of these cases a macroscopically detectable lesion existed, but apparently in none of them were serial sections made. More recently Biggart [2] has described 7 cases in which careful histologic study of the hypothalamus was carried out, with the result that in each instance destruction of the supraoptic-hypophysial tract was found. He called attention to the importance of such studies in other human cases and stated the belief that many of the cases previously reported would have been clarified by such analysis. In the present case a readily discernible lesion shown by serial section of the entire hypothalamus was degeneration of the supraoptic nucleus and tract. The case seems therefore worth recording in detail.

REPORT OF CASE

History.—C. A., an unmarried white man aged 30, an elevator operator, had considered himself well until he was 18 years of age (1926), when he had pneumonia (type II) associated with prolonged delirium. About one year after this infection, polydypsia and polyuria began, his daily intake of fluid being from 6,000 to 8,000 cc. Despite these symptoms he did not experience loss of weight, headaches or weakness and was able to lead a reasonably normal life until he was 26, when rather rapid loss of weight, from 140 to 121 pounds (63.5 to 54.9 Kg.), occurred. At that time an old, well healed tuberculous scar in the apex of the right lung and a 4 plus Wassermann reaction were discovered. After one and a half years of intensive antisyphilitic medication, his condition remained stationary until the development of an active bilateral pulmonary caseous tuberculous process about March 1939, during treatment for which he came under our observation.

There was no familial history of tuberculosis or diabetes insipidus.

When he was admitted to the hospital on Sept. 7, 1938, his chief complaints were chronic productive cough, weakness and loss of weight.

From the Departments of Medicine and Histology, New York Medical College and Flower Hospital, and the Medical Service of the Metropolitan Hospital.

1. Fink, E. B.: Diabetes Insipidus: A Clinical Review and Analysis of Necropsy Reports, Arch. Path. **6**:102 (July) 1928.

2. Biggart, J. H.: The Anatomical Basis for Resistance to Pituitrin in Diabetes Insipidus, J. Path. & Bact. **44**:305, 1937.

Examination.—The patient was thin, stoop shouldered, pale, cooperative and well oriented; he weighed 109 pounds (49.4 Kg.); his height was 68.5 inches (174 cm.), the distance from pubis to floor measuring 35½ inches (90 cm.). The left pupil was larger than the right; both reacted to light and in accommodation. The ocular fundi and visual fields were normal. The blood pressure was 100 systolic and 70 diastolic, and the pulse rate 96. The apexes of the lungs were sunken, and signs of a bilateral tuberculous process, with cavity formation, were evident. The temperature was normal until January 1939, after which it ran a septic course until his death on April 24, 1939.

The vital capacity of the lungs was 3,500 cc. The red blood cell count was 4,500,000 per cubic millimeter; the hemoglobin measured 80 per cent; the white blood cell count was 13,000 per cubic millimeter, with a differential count of 82 per cent polymorphonuclear leukocytes, 15 per cent lymphocytes and 3 per cent mononuclear leukocytes; the sedimentation rate of the erythrocytes was 28 mm. in fifteen minutes and 102 mm. in one hour. The Wassermann and Kahn reactions of the blood were strongly positive. The nonprotein nitrogen of the blood measured 34.4 mg. and the sugar 95.2 mg., per hundred cubic centimeters. A dextrose tolerance test (1.75 Gm. of dextrose per kilogram of body weight) revealed the following blood levels, expressed milligrams per hundred cubic centimeters: fasting, 94.3; one-half hour, 141.8; one hour, 185.2; two hours, 200.0, and three hours, 166.7. There was no glycosuria during the test. Examinations of the urine gave essentially normal results except for specific gravities persistently below 1.004. The basal metabolic rate was —10 per cent. Tubercle bacilli were routinely present in the sputum. Phenolsulfonphthalein excretion amounted to 75 per cent in two hours. The total protein in the blood serum amounted to 7.1 per cent, including 4.1 per cent albumin, 2.6 per cent globulin and 0.4 per cent fibrinogen. The results of restriction of fluid and sodium chloride are compared in the accompanying tabulation.

Approximate Daily Intake of Sodium Chloride (Gm.) for Three Days Prior to Test	Period in Hours	Fluid Intake, Cc.	Urine Output, Cc.	Comment
12	5.5	740	2,400	Thirst so intense that patient bolted out of bed to drink 1,680 cc. of water
1	6.0	750	1,700	Drank 700 cc. of water at completion of period

A similar response was obtained in a six day test in which the daily sodium chloride ration was 1.5 Gm. and there was an unrestricted fluid intake. At the end of this time the urinary volume was approximately 8 liters daily, as compared with 14 liters daily for a preceding control period of seven weeks (fig. 1). With increased ingestion of sodium chloride the patient showed a response in the blood content similar to that of the normal person. However, concentration of the salt in the urine was not increased, and a marked rise in minute output developed (fig. 2), in an effort to excrete the additional salt ingested.

Course.—The patient showed polyuria throughout his stay in the hospital. This was almost completely controlled for short periods by comparatively large amounts of solution of posterior pituitary twice U. S. P. strength (fig. 3), the dosage of which had to be reduced because of resulting abdominal distress.

During the first three months of hospitalization (until January 1939), the patient's pulmonary condition remained quiescent and the diabetes insipidus unchanged; his general condition improved, with a gain in weight of 7 pounds (3.2 Kg.). After this, and apparently as a result of advancing tuberculosis, his

temperature rose to as high as 102 F., his pulse rate varied between 116 and 130, and his weight dropped from 116 to less than 90 pounds (52.6 to 40.8 Kg.) just prior to his death.

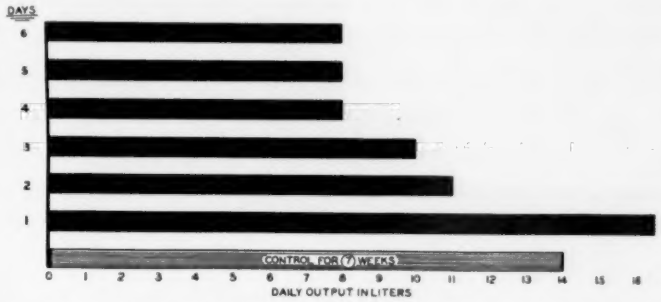

Fig. 1.—Effect of low salt ingestion (approximately 1.5 Gm. per day) on polyuria in a patient with diabetes insipidus.

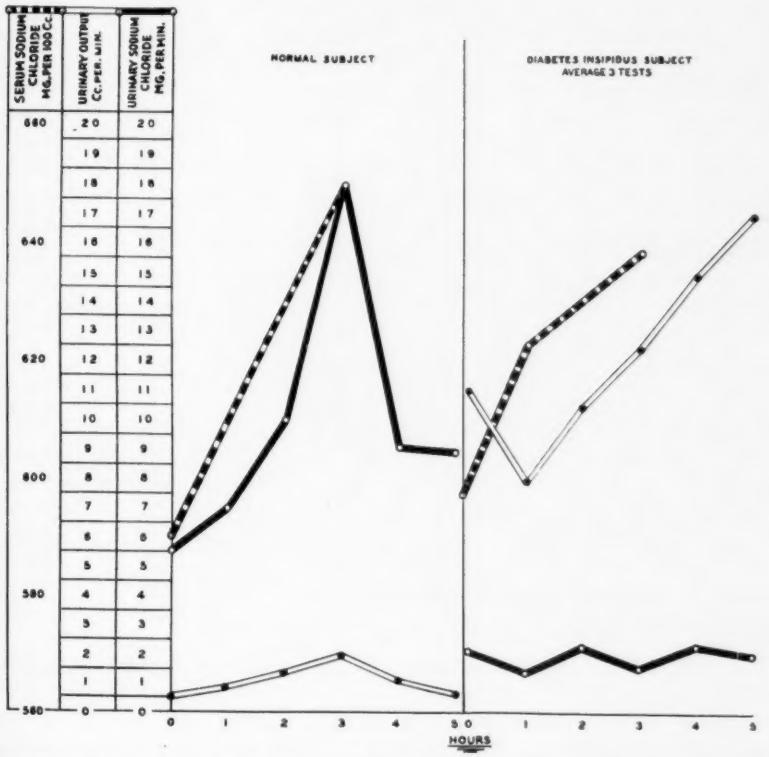

Fig. 2.—Effects of administering 0.25 mg. of sodium chloride per kilogram of body weight in a 10 per cent solution.

Necropsy.—Postmortem examination disclosed extensive bilateral caseous ulcerative tuberculosis of the lungs, with cavities in both apexes and almost complete obliteration of the entire parenchyma of the lower lobe of the right lung. The

two lungs together weighed 1,960 Gm. The heart was small, weighing only 188 Gm. The liver was firm and smooth, with sharp edges, and weighed 2,155 Gm.; on section the margins were obscured, and by reflected light the surface had a translucent, glassy appearance. The capsule of the spleen was tense and the organ firm and "rubbery"; on section the surface was light red and translucent.

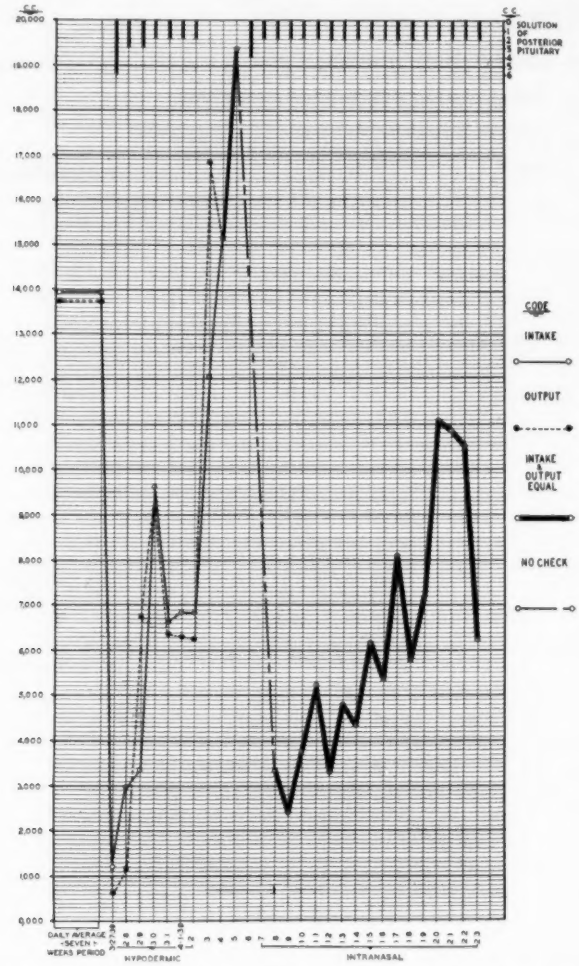

Fig. 3.—Effects of administering solution of posterior pituitary to a patient with diabetes insipidus.

The adrenal glands together weighed 18 Gm. and were golden yellow on transection. The kidneys weighed 190 and 170 Gm., respectively; were firm, and on cross section presented a glistening, light-reflecting surface, with sharply demarcated cortex and medulla. The brain showed no gross lesions. The pituitary gland was normal in size and shape and weighed 0.6 Gm.

Stained sections of the liver, spleen and kidneys showed large deposits of amyloid, for which tests with compound solution of iodine and hydrochloric acid gave positive reactions.

A block of tissue bounded anteriorly by the anterior commissure and posteriorly by the caudal border of the mamillary bodies and extending 8 or 10 mm. to the right and the left of the midline was removed from the brain, which had been fixed in formaldehyde, and was prepared for section.

Preparation of Hypothalamic Tissues.—The previously described block of hypothalamus from the patient's brain, hereafter termed "abnormal," was washed, dehydrated and then divided by midsagittal section before the left and right halves were embedded in paraffin.

The left half of this tissue was sectioned in the transverse plane, at 20 microns. The right half was sectioned in the sagittal plane, also at 20 microns. Alternate sections were mounted separately in each series, so that one section was stained with cresyl violet for cellular detail and the adjacent section by the Weil method for myelin sheaths.

A control series from an available block of the hypothalamus of similar dimensions from a normal human brain was prepared in the same way.

Results.—Sections were selected from the transverse series of the normal and abnormal brains which were stained for cells. The selected sections represent a level which passes through the middle portion of the supraoptic nucleus. This level is easily determined in the normal series, since the nucleus constitutes a clearly defined group of distinctive cells having a superficial position. These cells have been described and pictured in man and other mammals by Malone [3]; Greving [4]; Fisher, Ingram and Ranson [5]; Magoun and Ranson [6]; Hare [7]; Rasmussen,[8] and others.

Photographs of these sections from the transverse series of the normal and abnormal brains which were stained for cells are shown in reduction in figure 4 *A* and *B*.

Careful study of these and intermediate sections has convinced us that the supraoptic nucleus was completely absent in the abnormal hypothalamus. An equally careful examination of the right half of the abnormal hypothalamus, which was sectioned in the sagittal plane, failed to show any supraoptic nucleus on that side. A few of the more median sagittal sections of this brain were stained by Bodian's method, since the proximal stump of the infundibulum was

3. Malone, E. F.: The Nuclei Tuberis Laterales and the So-Called Ganglion Opticum Basale, Johns Hopkins Hospital Report Monograph 11, Baltimore, Johns Hopkins Press, 1914.

4. Greving, R.: Beiträge zur Anatomie der Hypophyse und ihrer Funktion: I. Eine Faserverbindung zwischen Hypophyse und Zwischenhirnbasis (Tr. supra-optico-hypophyseus), Deutsche Ztschr. f. Nervenh. **89**:179, 1926; Das Zentralnervensystem, in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927, vol. 4, pt. 1.

5. Fisher, C.; Ingram, W. R., and Ranson, S. W.: Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance: A Contribution to the Structure and Function of the Hypothalamico-Hypophyseal System, Ann Arbor, Mich., Edwards Brothers, Inc., 1938.

6. Magoun, H. W., and Ranson, S. W.: Retrograde Degeneration of the Supraoptic Nuclei After Section of the Infundibular Stalk in the Monkey, Anat. Rec. **75**:107, 1939.

7. Hare, K.: Degeneration of the Supra-optic Nucleus Following Hypophysectomy in the Dog, Am. J. Physiol. **119**:326, 1937.

8. Rasmussen, A. T.: Reaction of the Supraoptic Nucleus to Hypophysectomy, Proc. Soc. Exper. Biol. & Med. **36**:729, 1937.

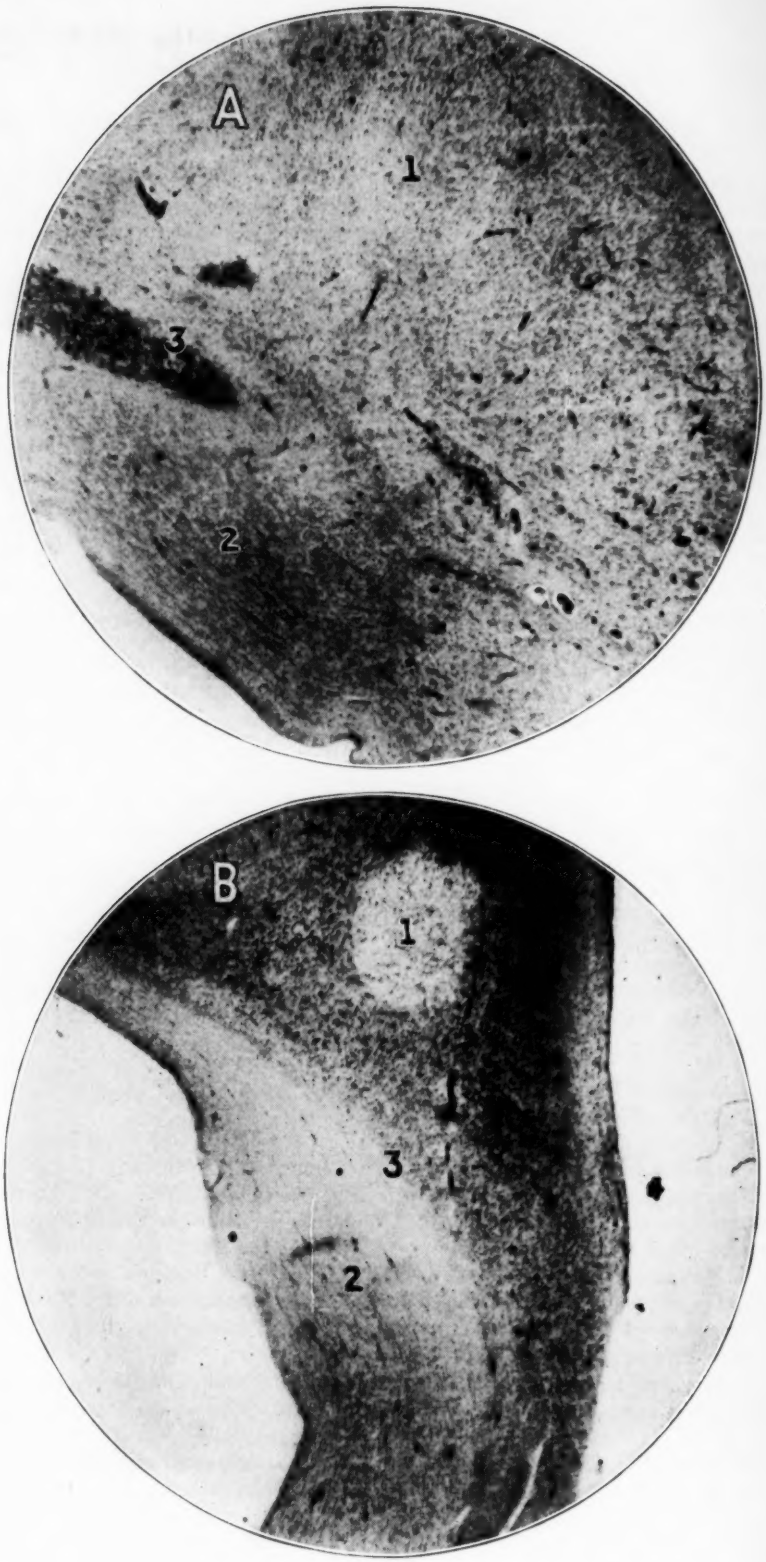

Figure 4

(See legend on opposite page)

attached. No clear evidence of a supraoptic-hypophysial tract could be obtained. The staining of these sections was unsatisfactory, however.

The pituitary gland of the abnormal brain was separated from the hypothalamus, having been somewhat distorted in the removal. This gland was similarly divided into right and left halves and sectioned in sagittal and transverse planes.

The anterior lobe and pars tuberalis, while shrunken as compared with the normal structures, appeared to contain a normal distribution of cells. The posterior lobe, however, was largely replaced by fibrous tissue, a limited area showing marked hypercellularity.

Anatomic Diagnoses.—The diagnosis was: bilateral caseous ulcerative tuberculosis of the lungs, to which death was attributed; amyloidosis of the liver, spleen and kidneys; tuberculous ulceration of the small and large intestines; degeneration of the supraoptic nucleus and of the posterior lobe of the pituitary gland, in association with diabetes insipidus.

COMMENT

In view of several recent comprehensive surveys of the subject of diabetes insipidus, both from the clinical [9] and from the experimental [10] viewpoint, it seems pertinent here to comment only on some of the features in the present case.

1. *Etiologic Factors.*—Any hereditary influence seems to be ruled out by virtue of the late onset of symptoms and the absence of other instances among the known members of the patient's family. Of the infections sustained by this man, tuberculosis made too late an appearance to be causative; moreover, postmortem examination revealed no intracranial lesions of a tuberculous nature. The time at which syphilis was contracted is not known. It is difficult to disprove its role in the degeneration observed in the supraoptic-hypophysial tract although no frank gross or microscopic syphilitic lesion was seen in the brain. In this connection, ependymitis granulosa should also be thought of. The delirium in association with the pneumonic infection may actually have been encephalitis, with which the association of type II pneumococcus was purely coincidental. Warkany and Mitchell,[9a] Whitehead and Darley [11] and Fink [1] found that encephalitis following a wide variety of infections gives rise to the syndrome of diabetes insipidus. However, in such instances, a cursory survey of the literature reveals that the

9. (*a*) Warkany, J., and Mitchell, A. G.: Diabetes Insipidus in Children: A Critical Review of Etiology, Diagnosis and Treatment, with Report of Four Cases, Am. J. Dis. Child. **57**:603 (March) 1939. (*b*) Staemmler, M.: Diabetes insipidus und Hypophyse, Ergebn. d. allg. Path. u. path. Anat. **26**:59, 1932. (*c*) Fink.[1] Fisher, Ingram and Ranson.[5]

10. (*a*) Biggart, J. H., and Alexander, G. L.: Experimental Diabetes Insipidus, J. Path. & Bact. **48**:405, 1939. (*b*) Fisher, Ingram and Ranson.[5]

11. Whitehead, R. W., and Darley, W.: A Case of Diabetes Insipidus Occurring as a Sequel to Epidemic Encephalitis, Endocrinology **15**:286, 1931.

EXPLANATION OF FIGURE 4

Fig. 4.—Photomicrographs of transverse sections of the left half of the hypothalamus through the middle of the rostrocaudal extent of the nucleus supraopticus. *1*, indicates the fornix; *2*, the optic tract, and *3*, the supraoptic nucleus. *A* is from a normal and *B* from an abnormal hypothalamus.

polydypsia and polyuria usually make their appearance during convalescence from the acute infectious process. In the present instance it would seem that at least one year elapsed between recovery from the encephalitis and the onset of the syndrome of diabetes insipidus.

2. *Polyuria.*—Most of the symptoms and all of the electrolytic disturbances of diabetes insipidus seem to be secondary to the profuse diuresis.[12] Richter and Eckert,[13] in rats, and Fisher, Ingram and Ranson,[14] in cats, have shown that polyuria invariably precedes polydypsia and that the latter is secondary to the former. The results of fluid deprivation tests performed in the present case are in keeping with the experimental results in animals. These show that the polyuria continues in the face of voluntary curtailment of the fluid intake. It has been possible to abolish the polydypsia in dogs by tying the ureters, in which instance the thirst disappeared.[13b] It has been suggested that the primary lesion of diabetes insipidus is the inability of the kidney to concentrate the urinary constituents. Karlson and Norberg [15] concluded that there is a "Typical disturbance in the capacity of the kidneys to concentrate both chloride and other constituents of the urine." The highly dilute urine, with low specific gravity, might at first thought warrant such a deduction. However, despite the enormous daily output of urine shown in some cases, including that of Whitehead and Darley [11] with an excretion of 30 liters, that of Rowntree,[16] with an excretion of 35 liters, that of Trousseau,[17] with an excretion of 43 liters, and our own, with a maximum of 22 liters, there is good evidence that the kidney tubules still have resorptive power. Cushing [18] has shown that an average of 60 to 75 liters of fluid pass through the renal glomeruli of a normal person in a single day. Therefore, even in the cases of severe polyuria just mentioned, a resorption of fluid and concentration of the glomerular filtrate of 50 to 75 per cent must have taken place in the tubules. Kennaway and Mottram [12a] found in cases of diabetes insipidus that urea was four times as concentrated in the urine as in the blood. Again, Forschbach and Weber [19] noted an increase of sodium

12. (*a*) Kennaway, E. L., and Mottram, J. C.: Observations upon Two Cases of Diabetes Insipidus, with an Account of the Literature Relating to an Association Between the Pituitary Gland and this Disease, Quart. J. Med. **12**:225, 1919. (*b*) Fisher, Ingram and Ranson.[5]

13. (*a*) Richter, C. P.: The Primacy of Polyuria in Diabetes Insipidus, Am. J. Physiol. **112**:481, 1935. (*b*) Richter, C. P., and Eckert, J. F.: Further Evidence for the Primacy of Polyuria in Diabetes Insipidus, ibid. **113**:578, 1935.

14. Fisher, C.; Ingram, W. R., and Ranson, S. W.: Relation of Hypothalamico-Hypophyseal System to Diabetes Insipidus, Arch. Neurol. & Psychiat. **34**:124 (July) 1935.

15. Karlson, S., and Norberg, B.: Normal Blood Chloride Variations and the Analysis of a Case of Diabetes Insipidus, Acta med. Scandinav. **88**:585, 1936.

16. Rowntree, L. G.: Studies in Diabetes Insipidus, J. A. M. A. **83**:399 (Aug. 9) 1924.

17. Trousseau, A.: Lectures on Clinical Medicine, translated by J. R. Cormack, ed. 3, London, New Sydenham Society, 1870, p. 528.

18. Cushing, H.: Papers Relating to the Pituitary Body, Hypothalamus, and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

19. Forschbach, B., and Weber: Beobachtungen über die Harn -und Salz-Ausscheidung im Diabetes insipidus, Ztschr. f. klin. Med. **73**:221, 1911.

chloride in the urine of more than 600 per cent in response to increased ingestion of salt, although the absolute value for the salt excreted remained low. It seems, therefore, that the polyuria represents not primarily a kidney defect but the more or less complete loss of some regulating substance or mechanism. Such a conception seems to have been reasonably well proved in the experimental laboratory by Ranson, Fisher and Ingram.[20]

Pitressin secreted by the posterior lobe (pars nervosa) of the pituitary gland is accredited with such controlling action. However, Walker[21] questioned its primary role in water regulation when he demonstrated that "pituitarectomized cats and rats continue to respond to water ingestion by water diuresis and to water deprivation by oliguria, in a fashion quantitatively similar to that which they exhibited before operation." Moreover, he stated the belief that he had detected an antidiuretic substance, not of pituitary origin, in quantities of physiologic significance.

3. *Behavior of Sodium Chloride.*—The diminution in polyuria more or less generally observed in either clinical or experimental diabetes insipidus after limitation of sodium chloride intake has led observers[22] to consider "some abnormality of sodium chloride metabolism" as the primary disturbance in diabetes insipidus. White and Findley[23] interpreted changes of the blood and urine in sodium chloride content similar to those seen in the present case (fig. 2) as "differences in sensitivity of the kidneys, presumably the tubules, to environmental changes." Fisher, Ingram and Ranson[5] stated the belief that the preponderance of evidence favors a direct action of the antidiuretic principle of the "pars nervosa" on the kidney structure. They expressed agreement with Peters[24] that the increase in reabsorption of water is by far the most striking effect of the hormone and "is out of all proportion to its influence upon the excretion of solutes." This conclusion would seem to be borne out by the salt-loading tests performed in the present instance. Blood levels of the salt varied as in the normal subject and total excretion was little different, but the maintenance of normal output was accomplished only by a tremendous increase in volume flow, rather than by urinary concentration, as it would have been in the patient without diabetes insipidus.

4. *The Anatomic Lesion.*—At first glance, the only causally related anatomic lesion which seemed to be present in the case under discussion was practically complete bilateral degeneration of the supraoptic nuclei

20. Ranson, S. W.; Fisher, C., and Ingram, W. R.: The Hypothalamico-Hypophyseal Mechanism in Diabetes Insipidus, A. Research Nerv. & Ment. Dis., Proc. (1936) **17**:410, 1938. Fisher, Ingram and Ranson.[5]

21. Walker, A. M.: Experiments upon the Relation Between the Pituitary Gland and Water Diuresis, Am. J. Physiol. **127**:519, 1939.

22. Swann, H. G.: Sodium Chloride and Diabetes Insipidus, Am. J. Physiol. **126**:341, 1939; Sodium Chloride and Diabetes Insipidus, Science **90**:67, 1939. Broers, H.: Experimentelle Diabetes insipidus, Utrecht, Kemink & Son, 1932.

23. White, H. L., and Findley, T., Jr.: Responses of Normal Subjects and of Patients with Diabetes Insipidus to Water and Salt Ingestion, J. Clin. Investigation **18**:377, 1939.

24. Peters, J. P.: Body Water: The Exchange of Fluids in Man, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

and the posterior lobe of the pituitary gland. Fisher, Ingram and Ranson [5] mentioned the reports of some 40 cases in which a "pure" hypothalamic origin of the diabetes insipidus was believed to exist. However, they commented "that few observers have detected the secondary hypercellularity and atrophy of the neural division after hypothalamic lesions or the secondary atrophy of the supraoptic nuclei, which might be expected to accompany those cases in which the neural division has been destroyed by various disease processes." Careful comparison of the pars nervosa with the same structure in normal brains has shown hypercellularity and some atrophy. The nuclei of the tuber cinereum have not suffered. According to Biggart,[25] this is an important finding, as in his analysis of 7 cases, the 4 patients who responded to treatment with solution of posterior pituitary had lesions only of the supraoptic-hypophysial tract, whereas those who were refractory to treatment showed involvement of the tuber cinereum as well. He stated the belief that syphilitic basilar meningitis and epidemic encephalitis were the etiologic factors in most of the cases in which there was resistance to the drug, but either may be present without altering the usual responses to solution of posterior pituitary. He called attention specifically to 25 cases in the literature in which resistance to the action of this substance existed.

This refractoriness to the administration of solution of posterior pituitary has been a point of departure in explaining the manner in which water control is regulated by hypothalamic activities. It is generally agreed that from 10 to 15 per cent of all patients with diabetes insipidus fail to react to the administration of solution of posterior pituitary. Biggart [25] claimed that his resistant patients had but one thing in common, namely, destruction of the nuclei of the tuber cinereum, in addition to the usual changes in the supraoptic-hypophysial tract. He stated the belief that if the substance acts directly on the kidney by way of the blood stream these persons should have responded to posterior pituitary therapy as completely as his other patients. He therefore postulated that the production of the antidiuretic principle of the posterior lobe is dependent on stimulation of the supraoptic nucleus or the supraoptic-hypophysial tract, whereas the antidiuretic action is mediated through effector pathways arising in the nuclei of the tuber cinereum. With such a hypothesis most workers are not in accord. Fisher, Ingram and Ranson,[5] on the basis of clinical and experimental evidence, stated that no such nerve mechanism accounts for the action of the hormone, although they had no acceptable explanation for the cases in which resistance to solution of posterior pituitary existed. They based this statement on the facts that (*a*) no patient is completely resistant to solution of posterior pituitary and (*b*) the pars nervosa fulfils all of the postulates necessary for it to be considered the organ responsible for secreting an active antidiuretic principle which acts by way of the blood stream, as well as on the denervated and isolated kidney.

Biggart and Alexander [10a] produced permanent polyuria in 14 dogs by bilateral destruction of the supraoptic nuclei or by interruption of their posterior hypophysial fibers at or anterior to the median eminence. This lesion was invariably followed by degeneration of the posterior lobe of the pituitary gland. Unfortunately, they did not put to experimental test their theory that patients with diabetes insipidus who are refractory

25. Biggart.[2] Biggart and Alexander.[10a]

to solution of posterior pituitary show, in addition to the foregoing lesions, selective destruction of the nuclei of the tuber cinereum.

5. *Interendocrine Relations.*—Several investigators [26] demonstrated aggravation in the status of the animal with diabetes insipidus by the feeding of thyroid and amelioration by thyroidectomy. Dix, Rogoff and Barnes [27] showed that the diuretic effect of thyroid feeding can be abolished in animals by pancreatectomy. Biggart and Alexander [10a] produced dramatic disappearance of polyuria by performing subtotal pancreatectomy in a dog with diabetes insipidus. Simultaneously, sensitivity to desiccated thyroid was lost, as much as 5 grains (0.32 Gm.) daily having no diuretic effect. Fisher, Ingram and Ranson [5] reviewed completely the evidence for the participation of the anterior lobe of the hypophysis in the regulation of water balance and concluded that this part of the hypophysis is the seat of formation of a diuretic hormone, antagonistic in its effects to that of the posterior lobe.

The foregoing facts are cited in relation to the present case. The anterior lobe of the hypophysis, the thyroid gland and the pancreas all appeared to be normal, grossly and microscopically, and were presumed, therefore, to have exerted normal physiologic influences. The severity of the disease can therefore be considered as varying directly with the extent of the lesions in the supraoptic-hypophysial system.

6. *Renal Impairment.*—Intrinsic disease of the kidney seems to be absent in cases of diabetes insipidus. Warkany and Mitchell [9a] remarked: "There is usually no albuminuria; and the nonprotein nitrogenous constituents of the blood, the elimination of phenolsulfonphthalein and the blood urea clearance are within normal limits." Kennaway and Mottram [12a] demonstrated the ability of the kidney to concentrate urea in a patient with diabetes insipidus. Our patient had no tendency to retain any waste materials in the blood stream and showed normal ability to excrete phenolsulfonphthalein.

7. *Effect of Drugs on Diuresis.*—Administration of solution of posterior pituitary caused a sharp reduction in urinary volume, from 14,000 to 650 cc., and a disproportionate but definite change in the specific gravity, from 1.000 to 1.009 (fig. 5). Clausen [28] was among the first to note that the change in the elimination of solutes is small as compared with the fluctuation in the volume of the urine as a result of administration of solution of posterior pituitary. The fact that the response in the present case was good may lend weight to the belief that the condition had its origin in postinfectious encephalitis rather than in an epidemic form.[29] Neither tolerance nor cumulative effects are to be

26. Barnes, B. O.; Regan, J. F., and Bueno, J. G.: Is There a Specific Diuretic Hormone in the Anterior Pituitary? Am. J. Physiol. **105**:599, 1930. Mahoney, W., and Sheehan, D.: The Effect of Total Thyroidectomy upon Experimental Diabetes Insipidus in Dogs, ibid. **112**:250, 1935. Footnote 10.

27. Dix, A. S.; Rogoff, J. M., and Barnes, B. O.: Diuresis of Hyperthyroidism, Proc. Soc. Exper. Biol. & Med. **32**:616, 1935.

28. Clausen, S. W.: The Effect of Injections of Pituitary Solution on the Urinary Output in a Case of Diabetes Insipidus, Am. J. Dis. Child. **16**:195 (Sept.) 1918.

29. Thompson, W. H.; Johnson, R. M., and McQuarrie, I.: Diabetes Insipidus: A Study of the Water and Mineral Exchanges, Am. J. Dis. Child. **46**:930 (Oct.) 1933.

noted, but unpleasant symptoms may necessitate a change in dosage or complete discontinuance of administration of the drug, as in our patient, who did not tolerate more than 2 cc. of solution of posterior pituitary of twice U. S. P. strength daily. Four cubic centimeters was necessary to keep the urinary volume within normal limits, and 6 cc. was even more effective. This seems contrary to Warkany and Mitchell's [9a] conception that amounts up to 3 cc. exert an effect which cannot be augmented by larger doses.

Ergot has been practically discarded in the treatment of diabetes insipidus, because of the variability in preparations made from it and because of its inconstant action on water balance. However, Lacy [30] reduced the urinary volume from 5 to 2 liters daily by its use.

Intermedin, material prepared according to the method originally described by Zondek, has been successfully used in 7 cases of diabetes insipidus,[31] although the response was not as great as that obtained with equal amounts of solution of posterior pituitary. The advantage of intermedin is its reputed freedom from pressor effects, a feature which would have made it a highly desirable substitute in the case here described.

Aminopyrine was given in the present case on several occasions to relieve headache, but never in doses of more than 10 grains (0.65 Gm.). Under such conditions its effect on diuresis was not appreciable. First Scherf [32] and later Kahn [33] and DeGowin [34] reported satisfactory reductions in urinary volume following the administration of 30 grains (1.9 Gm.) daily. However, the danger of agranulocytosis will probably prevent any widespread use of the drug in this country. DeGowin [34] found antipyrine effective in similar doses, but less antidiuretic. He saw no effect from other sedatives and anodynes, including acetophenetidin, acetylsalicylic acid, histamine, sodium bromide and morphine sulfate.

SUMMARY

A case of diabetes insipidus, probably secondary to postinfectious encephalitis, is reported.

Typical responses were obtained to ingestion and deprivation of water and salt and to administration of solution of posterior pituitary U. S. P. Bilateral degeneration of the supraoptic nuclei and the posterior lobe of the pituitary gland was the only notable lesion observed in the hypothalamus at necropsy.

30. Lacy, C. S.: Three Cases of Diabetes Insipidus Successfully Treated by Ergot, M. News **42**:9, 1883.

31. Sulzberger, M. B.: The Pituitary Hormone Intermedin as the Active Antidiuretic in the Treatment of Diabetes Insipidus: Preliminary Report, J. A. M. A. **100**:1928 (June 17) 1933. Turner, H. H.: Diabetes Insipidus: Treatment with Intermedin and Pitmelanin; Preliminary Report of Five Cases, Endocrinology **19**:275, 1935.

32. Scherf, D.: Pyramidon beim Diabetes insipidus, Wien. Arch. f. inn. Med. **22**:457, 1932.

33. Kahn, B. S.: The Use of Amidopyrine in a Case of Diabetes Insipidus, J. A. M. A. **100**:1593 (May 20) 1933.

34. DeGowin, E. L.: The Urinary Concentration in Diabetes Insipidus: A Comparison of the Effects of Several Drugs, Am. J. M. Sc. **190**:747, 1935.

RESORPTION OF INTRACRANIAL GUMMA UNDER ELECTROENCEPHALOGRAPHIC CONTROL

MARGARET RHEINBERGER, PH.D., AND JOSEPH SIRIS, M.D., NEW YORK

Resolution of intracranial gummas, as evidenced by roentgen study, is not uncommon. Alteration of the position of the calcified pineal body or of the pneumencephalographic picture attendant on diminution in size or disappearance of such lesions has been described. An example of the former was cited by Bailey.[1] His patient showed improvement in symptoms, recession of papilledema and return of the pineal body to the midline three months after inauguration of treatment with bismuth and iodides. Paleari [2] recorded an instance of marked cerebral ventricular shift in which the ventricles returned to normal position after the institution of antisyphilitic therapy.

The problem of intracranial gummas, however, is not invariably handled with such facility. When the neurosurgeon is confronted with evidence of intracranial hypertension, rapidly failing vision, advancing papilledema and a positive Wassermann reaction of the blood or cerebrospinal fluid, he cannot always temporize until a diagnosis is definitely established; or, even having decided that the clinical picture is entirely on a syphilitic basis, he may find it impossible to preserve vision without decompression, despite vigorous antisyphilitic therapy. It was the teaching a generation ago that in most cases of increased intracranial pressure the condition was syphilitic and that the patient should be given intensive antisyphilitic treatment. The more recent trend is in the opposite direction, that of surgical removal of intracranial tumors even when they are known to be gummas, on the basis of the surer preservation of vision and the allegedly easier response to the subsequent antisyphilitic therapy.

Locke [3] pointed out that syphilitic leptomeningitis, as well as gumma, can be responsible for intracranial hypertension. His suggestion that a subtemporal decompression be carried out when signs of increased pressure do not promptly subside after antisyphilitic therapy has been adopted by many neurosurgeons. The interest of the case presented in this report stems from the fact that it suggests a middle ground of conservative treatment in selected cases. Were it possible to follow roentgenographically the progress in such cases, the utility of medicinal therapy could be evaluated more satisfactorily than has been possible

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From the Department of Neurosurgery, the Jewish Hospital of Brooklyn.

1. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933, pp. 398-399.

2. Paleari, A.: Processo cerebrale luetico a rapida risoluzione. Reperto encefalografico prima e dopo la terapia, Policlinico (sez. prat.) **45**:525-533, 1938.

3. Locke, C. E., Jr.: Increased Intracranial Pressure Associated with Syphilis, Arch. Surg. **18**:1446-1462 (April) 1929.

up to the present, but it is not possible in all instances to observe a shift of the calcified pineal body, nor is it always feasible to follow such progress by means of the pneumencephalogram. A simple yardstick of progress permitting a wide margin of safety for the patient is afforded by electroencephalographic control, if the results obtained in the case reported in this paper are confirmed in subsequent investigations.

The following case is reported in detail not only because of the particular interest already mentioned, but also because of the somewhat unusual course.

REPORT OF A CASE

Clinical evidence of expanding lesion in the left frontal lobe; advanced papilledema; strongly positive Wassermann reactions of the blood and cerebrospinal fluid; electroencephalographic and pneumencephalographic evidence of a lesion in the left frontal lobe. Antisyphilitic therapy, with subsequent improvement in symptoms and signs and coincident return to normal of the electroencephalogram and pneumencephalogram.

History.—N. H., a Negress aged 22, a domestic worker, was admitted to the Jewish Hospital of Brooklyn on Jan. 19, 1939. Two months prior to her admission she had first been troubled with left frontal headaches of progressively increasing severity, which were apt to be worse in the morning and tended to radiate over the left ear to the back of the neck. About three weeks after the onset of headache, the patient began to suffer from intermittent diplopia and progressive impairment of visual acuity, involving both eyes. Vomiting occurred on one occasion, the morning of admission. The familial and past histories were irrelevant.

Examination.—The temperature was 99.8 F., the pulse rate 74, the respiratory rate 28 and the blood pressure 110 systolic and 68 diastolic.

The patient was considerably distraught by headache, but memory, orientation and internal speech function were undisturbed. Significant physical findings included exquisite tenderness to percussion over the left frontal region, right internal strabismus, moderately advanced bilateral papilledema, with hemorrhages and stellate areas of exudate in both macular regions; diminished activity of the right abdominal reflexes as compared with the left, and generally sluggish deep reflexes. The visual fields showed generalized constriction. Visual acuity was 20/20 in the right eye and 20/70 in the left eye. Coordination, motor power and sensation were within physiologic limits. The patient was left handed.

Laboratory Data.—At the time of admission the blood count, blood chemistry studies and urinalysis revealed nothing of particular significance. The erythrocyte sedimentation rate was 60 mm. per hour. Kline and Wassermann reactions of the blood were strongly positive. Examination of the cerebrospinal fluid revealed an initial pressure (after subtemporal decompression) of 306 mm. of water, an Ayala index of 5.3, 10 lymphocytes and 10 polymorphonuclear cells per cubic millimeter, a Wassermann reaction of 4 plus, a normal colloidal gold curve, 131 mg. of protein and a 1 plus reaction for globulin. Roentgenograms of the skull showed essentially normal structures.

Electroencephalogram.—An electroencephalogram made on January 21 (fig. 1) disclosed abnormal irregular, slow waves in the left frontal region. The maximum discharge was localized within an area, the radius of which was about 4 cm., surrounding a point 6 cm. to the left of the midline and 8 cm. posterior to the lateral border of the left eyebrow. Only slight deviations from an irregular but otherwise essentially normal electrical pattern were observed in tracings from regions outside this area, as shown in figure 1 (Dr. Rheinberger).

Operation.—Because of the advanced papilledema, it was deemed advisable to carry out subtemporal decompression on the right side for preservation of vision before undertaking further studies. This was accordingly done on January 23, with the region under local anesthesia. The area of brain exposed was moderately edematous and bulged slightly through the dura mater when the latter was opened.

Course.—After operation the patient was given potassium iodide, three times daily, and bismuth salicylate. An electroencephalogram taken eight days after the operation and the institution of antisyphilitic therapy (fig. 1) disclosed electrical abnormalities similar to those previously observed, but of much lower amplitude and diffused over a somewhat wider area medially and posteriorly (Dr. Rheinberger). Only a single dose of bismuth salicylate had been given at the time of these readings.

Convalescence was uncomplicated until the tenth day after operation, when the patient complained of "drawing" pain in the right popliteal space. On the following day there were marked weakness of the right extremities, weakness of the right external rectus muscle and weakness of the right facial nerve, of central type. The deep reflexes of the right half of the body were more active than those of the left. Below the sixth thoracic dermatome on the right there was marked impairment of all modalities of sensation. Papilledema at that time was unchanged. To establish more definitely the nature of the lesion, a pneumencephalogram was made on February 6, two weeks after the operation (fig. 2 *A*). This revealed displacement of the lateral ventricles to the right. At this time the Wassermann

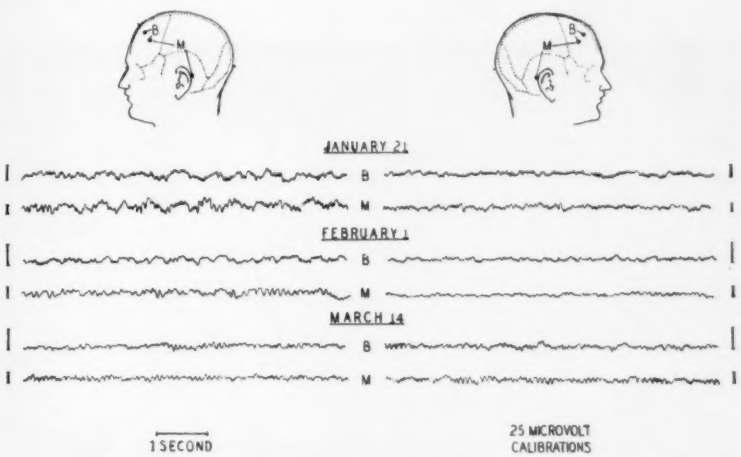

Fig. 1.—Simultaneous electroencephalographic records from the left and the right frontal regions, with both bipolar (*B*) and mastoid (*M*) leads.

The record for January 21 was made on admission; that for February 1 was taken eight days after right subtemporal decompression and institution of antisyphilitic therapy, and that for March 14, seven weeks after the institution of antisyphilitic therapy.

It should be noted that the slow potentials recorded from the left side on January 21 are of less magnitude in the record for February 1 and do not appear in that for March 14.

reaction of the cerebrospinal fluid was negative and the colloidal gold curve was likewise normal. The Kline and Wassermann reactions of the blood were still strongly positive.

The patient showed some improvement under medicinal therapy, so that by February 23 she was able to sit in a chair. Other findings on that date included slight tension and swelling of the area of decompression and unchanged papilledema. Visual acuity was 20/100 in the right eye and 20/70 in the left. Estimated impairment of motor power of 40 per cent was present in the right extremities. The deep reflexes of the right half of the body were still slightly more active than those of the left. Pain and vibratory sensibility were moderately diminished on the right side of the body.

An initial dose of 0.2 Gm. of neoarsphenamine was administered on February 24. On the following day the patient complained of pain over the lower thoracic portion of the spine, the left costovertebral region and the left lower part of the chest. Roentgenograms of the region of the lumbodorsal part of the spine revealed

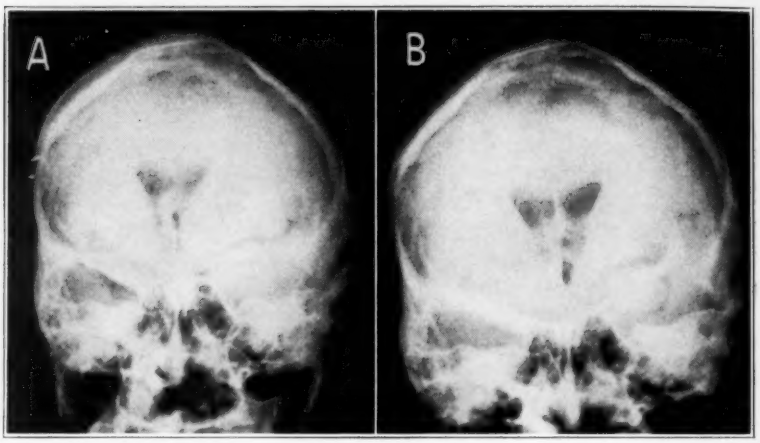

Fig. 2.—Pneumencephalograms obtained at the beginning and conclusion of antisyphilitic therapy.

A, made on February 6, shows the ventricular system shifted to the right; *B*, on April 1, shows a normal ventricular system.

nothing abnormal. Two days later the patient complained of pain in the lower right abdominal quadrant, associated with active vomiting. The abdomen was diffusely tender, with tenderness maximal over McBurney's point. There was no definite rigidity. Diffuse tenderness was elicited by rectal examination. The white blood cell count was 10,350, with 76 per cent polymorphonuclears. It could not be established with certainty whether the patient's pain was due to a Herxheimer reaction, a tabetic crisis, acute appendicitis or a cerebral lesion. It was the consensus that although acute appendicitis was unlikely, one could not safely temporize. Accordingly, appendectomy was performed on February 27. Examination of the appendix revealed marked hyperplasia of the lymphoid elements.

Another electroencephalogram was made on March 14, seven weeks after the inauguration of antisyphilitic therapy (fig. 1). The record at that time showed nothing which could be called a specific electrical abnormality. There was a

possible irregularity in the tracings from the left occipital region, which was of doubtful significance (Dr. Rheinberger). At this time the Kline and Wassermann reactions of the blood were still strongly positive. Advanced papilledema was still present.

Pain in the back and the abdomen persisted. On March 14 the patient experienced particularly sharp pain in the right flank, radiating into the ipsilateral groin. Occasional hematuria was reported. Urologic investigation disclosed marked congestion in the region of the trigon and double pelvis and ureter on the right, with slight hydronephrosis. The right kidney appeared definitely larger than average. There was no evidence of calculus in the right urinary tract. A specimen of vesical urine was free of cells and showed gram-negative bacilli on smear and colon bacilli on culture. A specimen taken from the right kidney was normal.

A slight amelioration of symptoms followed. A check-up on March 27 revealed that the patient was still suffering from pains in the head, chiefly in the left frontal region. The papilledema had receded appreciably. The area of decompression was flat. Impairment of motor power of about 20 per cent was still present in the right extremities. The deep reflexes were suppressed generally, except for the ankle jerks. Cutaneous sensibility was still diminished on the right side of the body. Vibratory sensibility was diminished in the lower right extremity and in the vertebral spine below the midthoracic region.

By April 1 the patient's condition had improved sufficiently to permit further pneumencephalographic study (fig. 2 *B*). This revealed that the displacement of the ventricular system to the right was no longer present and that the ventricles were now in their normal position. By April 6 papilledema was practically gone; the optic nerve heads were a good pink, and the temporal margins were fairly clear. The Kline reaction of the blood on the following day was normal, as were the Wassermann reaction of the cerebral spinal fluid and the colloidal gold curve. By April 14 the patient was free of symptoms. Objectively, one could demonstrate weakness of the right extremities (about 20 per cent impairment). All forms of sensibility were diminished below the first lumbar dermatome on the right. The reflexes, both superficial and deep, were sluggish. Slight tenderness was still present in the area over the left frontal lobe.

COMMENT

Perusal of this report reveals many provocative features. Of incidental interest is the problem of the relation of tumor of the brain and syphilis of the central nervous system exemplified by this study. When the patient was first seen, a diagnosis could not be definitely established. The possibilities considered included coexistent intracranial tumor and syphilis; syphilis of the central nervous system with secondary papilledema on the basis either of intracranial gumma or of basilar syphilitic meningitis, and intracranial tumor with a secondarily positive Wassermann reaction. The persistently normal colloidal gold curve argued strongly against the possibility of parenchymatous involvement of the central nervous system by syphilis.

In this connection, observations previously recorded in the literature are of interest. Moersch [4] cited Lange [5] as authority for the statement

4. Moersch, F. P.: Tumors of the Brain and Syphilis, Am. J. M. Sc. **175:** 12-18, 1928.

5. Lange, C.: Was leistet die reine Liquordiagnostik bei der Diagnose des Hirntumors? Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33:**582-610, 1921.

that "a positive Wassermann reaction on the spinal fluid in a case of brain tumor is of little value as it may result from the increase of albumin, which produces a nonspecific reaction." Of a series of about 1,000 cases of definitely established tumor of the brain, exclusive of intracerebral gummas, seen at the Mayo Clinic, Moersch noted positive Wassermann reactions of the blood in 18. In most of these cases the positive reaction was verified by repeated examination. In only 4 of the 18 cases could the possibility of syphilis be considered. The Wassermann test of the cerebrospinal fluid was made in 11 of the 18 cases and gave a positive reaction in 1 instance. In 1 case in the series the reaction of the cerebrospinal fluid was positive and that of the blood negative. Positive Wassermann reactions of the blood [6] and of both the blood and the cerebrospinal fluid [7] in cases of tumor of the brain have been reported by other observers.

It is important that the association of papilledema and positive serologic reaction should not necessarily be interpreted as indicating syphilis rather than a tumor of the brain. Moersch pointed out that the diagnosis of syphilis in cases of brain tumor is made more frequently than that of brain tumor in cases of syphilis. In his series, when syphilis of the nervous system existed in association with papilledema and other evidences of cerebral tumor, patients either improved or recovered under treatment and there was no further evidence of tumor. The serologic data, the condition of the fundus or any one cardinal symptom, according to Moersch, is not pathognomonic of either tumor of the brain or syphilis.

Of particular interest in the present study is the fact that combined pneumencephalographic and electroencephalographic evidence pointing to the disappearance of a large mass lesion (probably a gumma) was available. Use of the pneumencephalogram as a diagnostic aid is probably not without danger when intracranial hypertension exists, and the procedure is too formidable to be repeated with the frequency required for accurate evaluation of the efficacy of antisyphilitic therapy. Too long a delay in arriving at a decision as to whether antisyphilitic therapy should be continued alone or should be supplemented or replaced by surgical intervention unduly jeopardizes the vision and life of the patient. Since the serologic test is not necessarily of value in establishing a diagnosis or in guiding therapy, it is obviously essential to have some instrument by which the efficacy of antisyphilitic therapy can be recorded promptly. To our knowledge, this is the first time the electroencephalo-

6. (*a*) Marburg, O.: Beitrag zur Frage der Kleinhirnbruckenwinkeltumoren, Neurol. Centralbl. **29**:570-572, 1910. (*b*) Lange.[5] (*c*) Stern, F.: Ueber positive Wassermannreaktion bei nichtluetischen Hirnerkrankungen, Arch. f. Psychiat. **61**: 725-734, 1920. (*d*) Kaplan, D. M.: Serology of Nervous and Mental Diseases, Philadelphia, W. B. Saunders Company, 1914.

7. (*a*) Newmark, L.: The Occurrence of a Positive Wassermann Reaction in Two Cases of Nonspecific Tumor of the Central Nervous System, J. A. M. A. **58**:11-13 (Jan. 6) 1912. (*b*) Lotmar, F.: Zur Kenntnis der Wassermann-Reaktion bei Tumoren des Zentralnervensystems, Schweiz. med. Wchnschr. **51**: 1013-1016, 1921. (*c*) Stern.[6c]

gram has been utilized successfully for this purpose.[8] Its use in this case not only permitted control of the therapeutic regimen but aided in establishing a diagnosis which otherwise would have been uncertain. Confirmation of the electroencephalogram by the pneumencephalographic findings suggests the possibility of the substitution of the former for the latter in the determination of the presence and response to therapy of intracranial gummas.

8. The accumulating evidence on the usefulness of the electroencephalogram in the recognition and localization of cerebral abnormalities need not be detailed here. The reader is referred to the papers of Case and Bucy (Localization of Cerebral Lesions by Electro-Encephalography, J. Neurophysiol. **1**:245-261, 1938); Williams and Gibbs (Electroencephalography in Clinical Neurology: Its Value in Routine Diagnosis, Arch. Neurol. & Psychiat. **41**:519-534 [March] 1939), and Walter (Critical Review: The Technique and Application of Electroencephalography, J. Neurol. & Psychiat. **1**:359-385, 1938).

It should be emphasized that the electroencephalogram obtained in this case is not specifically indicative of the type of lesion involved. The disturbance in the normal electrical pattern caused by a gumma will undoubtedly depend on the same factors as those obtaining in other tumors, i. e., the extent of cortical damage and the location relative to the usual placement of electrodes on the surface of the scalp.

Abstracts from Current Literature

Physiology and Biochemistry

THE REGULATION OF THYROTROPIC FUNCTION BY THYROXIN AFTER PITUITARY STALK SECTION. U. U. UOTILA, Endocrinology **26**:129 (Jan.) 1940.

An increase or a decrease in the thyroxine level is believed to act on the anterior lobe of the pituitary gland without the mediation or modifying action of the pituitary stalk. Thyroxin given to male rats in daily doses of 5 mg. per kilogram of body weight for ten days caused marked atrophy of the thyroid whether the pituitary stalk was severed or intact. Furthermore, other effects produced by injection of thyroxin, such as loss of weight, cytologic changes in the anterior lobe of the pituitary gland, hyperplasia of the adrenal cortex and atrophy of the seminal vesicles, were similar in animals in which the stalk was cut and in animals in which it was intact. Residual thyroid tissue was still capable of compensatory hyperplasia after subtotal thyroidectomy, even after the pituitary stalk had been destroyed. Uotila concludes that the thyrotropic function of the anterior lobe of the hypophysis has a basic secretory rhythm which is for the most part controlled humorally by variations in the organism's thyroxine level without the mediation of the hypothalamohypophysial pathways. Hypothalamic impulses through the pituitary stalk, or to a lesser extent the cervical portion of the sympathetic trunk, can under certain conditions modify this basic thyrotropic secretory rhythm.

PALMER, Philadelphia.

THE GONADOTROPIC HORMONE OF URINE OF PREGNANCY. S. GURIN, C. BACHMAN and D. W. WILSON, J. Biol. Chem. **133**:467, 1940.

Purified gonadotropic hormone from the urine of pregnant women appears to be composed chiefly of glycoproteins. The nonhexosamine carbohydrate is galactose. The molar ratio of galactose to hexosamine (2:1) suggests that the carbohydrate portion of the molecule is built up of hexosamine digalactose units. The amino group of the hexosamine appears to be acetylated, and another acetyl group is attached elsewhere in the molecule. The hormone has no serologic relation to the blood group A-specific polysaccharide.

PAGE, Indianapolis.

CHEMICAL STUDIES ON THE PITUITARY "ANTAGONIST." F. BISCHOFF, J. Biol. Chem. **133**:621, 1940.

There is present in extracts of the anterior lobe of the pituitary a fraction which when given intraperitoneally antagonizes the action of gonadotropic agents. In disagreement with the observations of others, Bischoff finds that follicle stimulation can be promoted by intraperitoneal injection of pituitary extracts containing the gonadotropic principle; the "antagonist" effect can be produced by subcutaneous injection. Either effect is produced by regulation of the rate of resorption. No difference in response to a wide range of chemical reactions was found between the "antagonist" and the gonadotropic factor. The responses included acetylation; methylation, and reactions to betanaphthoquinone sulfonate, iodine, diazobenzene sulfonate, cysteine and heat treatment. The existence of the luteinizing and the "antagonist" fraction as separate and distinct hormones is not borne out by these observations.

PAGE, Indianapolis.

GRASPING AND SUCKING. IRVING BIEBER, J. Nerv. & Ment. Dis. **91**:31 (Jan.) 1940.

Although the grasp response may be inconstant in the newborn child, it is facilitated by the act of sucking and by tension on the muscles of the upper limb. The feeding infant clutches its mother, and grasping frequently endures until sucking ceases. Facilitation of the sucking reflex by the act of grasping is also demonstrable in infants, although less easily. Thus, in the newborn child the grasp response serves the mechanism of support and insures maintenance of posture during feeding. The receptor area for the sucking reflex originally includes the tongue and the mucous membranes, but in a few days it broadens to include, in order, the lips, the angles of the mouth, the chin and the cheeks. The fully developed response involves pouting, opening the mouth, turning the head to bring the mouth to the object and actual sucking. Later organization adds hand to mouth movements at the fifth month and prehension at the ninth month. More complete organization of the nervous system results in inhibition of these automatic responses in favor of more complex behavior patterns. Grasping reappears in the adult when, for any reason, posture cannot be mediated by the normal mechanism, so that the hands must reassume their supportive role, or when there is disintegration of the function of the central nervous system.

Bieber reports the case of a man with multiple cerebral softenings in whom the complete sucking response reappeared, the stimulus including either visual or tactile elements. A grasp reflex was present bilaterally and was facilitated by the sucking reflex. Thus, the interrelationships of the sucking and grasping responses were illustrated in a patient in whom disintegration of the function of the central nervous system had occurred. Experimental work has shown that interference with the function of the premotor cortical area causes reappearance of the grasp reflex. The return of the sucking response also reflects a serious disintegration of function, and the more complete the disorganization the more nearly does the adult sucking revert to the infantile level.

MACKAY, Chicago.

IMPULSES IN THE PYRAMIDAL TRACT. E. D. ADRIAN and G. MORUZZI, J. Physiol. **97**:153, 1939.

In an extensive report, the authors describe observations on action potentials in the pyramidal tracts for comparison with surface potentials in the cerebral cortex. The potentials in the pyramidal fibers were picked up with needle electrodes inserted into the medulla at the level of the pyramidal decussation. The results of the study follow: 1. In the anesthetized cat, except when under the deepest anesthesia, there is persistent spontaneous activity in the motor system, and discharge of impulses in the pyramidal fibers corresponds closely with that of potentials in the motor area (sigmoid gyrus). With dial anesthesia, the cortical waves occur in groups at a rate of 7 to 10 a second, and the impulses in the pyramidal tract are grouped in the same way. With ether anesthesia the frequency of the cortical waves often rises to 40 to 60 per second, and the pyramidal discharge has the same frequency. 2. With a fine wire electrode the action potentials can be recorded in single conducting units of the pyramidal tract (a single axon or groups acting in unison). The discharge in the single unit agrees in frequency with the cortical potentials, the impulses occurring at a rate of 7 to 10 per second with dial and of 40 to 60 per second with ether. Sometimes, instead of a single impulse there is a group of two or three closely spaced. 3. Under unfavorable conditions, such as low blood pressure, the pyramidal discharge may fail, although surface potential waves can still be recorded from the motor area. Temporary dissociation can be produced by a period of cerebral anemia. 4. With the use of lighter anesthesia sensory stimulation often causes an increase in the pyramidal discharge, the frequency in single units rising to from 50 to 150 per second. The discharge is sometimes accompanied by movement of a limb. The frequency varies over a wide range, and there is no tendency to one or more fixed values. 5. With a compound of chloral hydrate and dextrose (chloralose), an

abrupt stimulus will produce a convulsive movement. The reaction involves the motor cortex and is due to a sudden discharge of impulses in the pyramidal fibers. It is often followed by a longer series of impulses, with a frequency which varies with the intensity of the stimulus from 10 to 200 per second. 6. Records like those from the pyramidal decussation can be obtained from the white matter of the motor cortex, but the origin of the impulses is less certain, as the white matter contains fibers from other parts of the brain. 7. Low frequency discharges in the pyramidal fibers produce no obvious motor effects (movement or change of tone). To become supraliminal for the motor nerve cells of the spinal cord, the discharge must exceed a threshold intensity, whether the cord is affected by the anesthetic or not. 8. When convulsant drugs, such as strychnine or picrotoxin, are injected or applied locally to the motor cortex, the pyramidal discharge takes the form of a series of high frequency outbursts, the impulses in each unit occurring in groups of 10 to 80 at frequencies of 500 to 1,000 per second. 9. The outbursts seem to be made up of prolonged repetitive discharges from the Betz cells, due to an abnormally slow decline in each period of activity. Some of the action potentials are due to several neurons working in phase. It is unlikely that the outburst is due to a wave of excitation spreading over a series of Betz cells and making each discharge one impulse. 10. With convulsant drugs, sensory stimulation produces the high frequency outbursts before they begin to occur spontaneously, and when they occur spontaneously they can be produced at shorter intervals by stimulation. 11. High frequency outbursts in the pyramidal fibers, when fully developed, produce convulsive movements except when anesthesia is very deep. This type of discharge seems to be especially capable of overcoming the synaptic resistances in the spinal cord. 12. Electrical stimulation of the motor cortex may produce movement because each shock sets up a brief high frequency discharge. The number of impulses to a single shock increases in each unit as facilitation develops, and there is an increase in the number of units in action. Weak stimuli at lower frequencies (30 per second or less) may send single impulses down the pyramidal fibers, but the discharge is subliminal for the cord and no movement results. 13. After electrical stimulation there may be an after-discharge of high frequency outbursts, associated with clonic movements if the anesthesia is not too deep. This is succeeded by a period of complete inactivity. It is suggested that the phenomena of "extinction" may be due to this period of exhaustion following activity. 14. The aforementioned results have been obtained from the anesthetized cat. There is reason to think that in the normal animal the pyramidal discharges could be maintained at high frequencies for longer times, but that they would show the same wide variation in frequency, depending on the degree of excitation of the cortex.

THOMAS, Philadelphia.

THE PRODUCTION OF EXOPHTHALMOS IN THE DOG BY ACETYLCHOLINE. CHARLES E. BRUNTON, J. Physiol. **97**:383, 1940.

Brunton undertook to determine the mechanism of exophthalmos produced by acetylcholine. Injections of acetylcholine were made under anesthesia induced with a compound of chloral hydrate and dextrose (chloralose) in dogs from which one superior cervical sympathetic ganglion had been removed either at the time of operation (series 1) or sufficiently long before to allow degeneration of the nerves which supply Müller's orbital membrane (series 2). The injections produced about the same amount of exophthalmos on the denervated side as on the side on which the ganglion and its nerves were intact. Hence, they affected the orbital membrane or the orbital vessels or both.

By perfusing isolated dogs' heads, it was possible to provide a constant blood supply to the orbits. Under this condition acetylcholine produced exophthalmos in only 2 of 27 cases in which the ganglion had been removed. This and other evidence leads to the conclusion that the main action of acetylcholine in the intact animal is relaxation of blood vessels. The relaxed vessels are then distended with blood and push the eyeball forward.

THOMAS, Philadelphia.

ELECTRIC INTERACTION BETWEEN TWO ADJACENT NERVE FIBERS. B. KATZ and O. H. SCHMITT, J. Physiol. **97**:471, 1940.

Katz and Schmitt stimulated one of a pair of large nonmedullated axons isolated from the limb nerve of the crab and observed the effects of the resulting action potentials on the other axon. They found that as the potential wave in the active axon approaches a given point, the excitability of the resting fiber at that point is at first reduced, then quickly increased above normal and finally slightly depressed for a second longer period. When both fibers are stimulated simultaneously a mutual interaction between the action potentials takes place, producing various combinations of speeding and slowing, depending on the phase relationship between the two impulses. The general tendency is to speed up the slower impulse, so that if the rates of conduction differ only slightly the impulses are synchronized. The quantities of the observed effects are of an order of magnitude consistent with the electrical theory of nerve conduction. The external effects of the action potentials are small and do not tend to cause independent stimulation of adjacent fibers; hence "isolated conduction" is the rule.

THOMAS, Philadelphia.

THE BLOOD PHOSPHORUS IN EPILEPSY. F. P. DEL RONCAL, Arch. de neurol. y psychiat. de Mexico **3**:451, 1939.

Del Roncal found that the normal value for the total phosphorus content of the blood was about 370 mg., that for the mineral phosphorus content of the blood 33 mg. and that for the mineral phosphorus content of the plasma 32 mg., per thousand cubic centimeters. Of 50 patients with epilepsy, 36 per cent showed increase in the amount of total phosphorus in the blood. Of a series of 31 patients, the mineral phosphorus of the blood was increased in 8 and that of the plasma in 5. A further study of the 31 patients with abnormal phosphorus content revealed that 16 patients were demented, 1 had pseudodementia, 4 showed mental debility and 10 were in good physical condition. Of the patients with normal phosphorus, 13 were in good physical condition, 4 showed mental debility and 2 pseudodementia. Del Roncal concludes that phosphorus in the blood is increased in epilepsy, that the increase is related to the clinical state of the patient and that attacks seem to augment the amount of phosphorus in the blood.

NORCROSS, San Francisco.

RETARDATION OF FATIGUE PRODUCED BY VITAMIN B_1. H. J. BRIEM, Arch. f. d. ges. Physiol. **242**:450, 1939.

In order to test Minz's theory that vitamin B_1 activates acetylcholine, Briem studied the effect of vitamin B_1 on acetylcholine contracture and on muscular fatigue in isolated frog muscles (rectus abdominis; sartorius). The addition of vitamin B_1 to Ringer's solution markedly increased the acetylcholine contracture and retarded fatigue. The concentrations of vitamin B_1 necessary for these effects, however, were high (2,000 micrograms per hundred cubic centimeters of solution), and beyond the physiologic range. If phosphates are added to the Ringer solution, corresponding to the normal concentration of the serum (12 mg. per hundred cubic centimeters), these effects may be obtained with physiologic values of vitamin B_1 (10 to 100 micrograms per hundred cubic centimeters). The addition of phosphates increases the danger of overdosage of vitamin B_1. The experiments suggest that vitamin B_1 may be tried in treatment of myasthenia.

SPIEGEL, Philadelphia.

MOTOR AUTOMATISMS IN SKIING. W. BIRKMAYER and K. SCHINDL, Arch. f. d. ges. Physiol. **242**:456, 1939.

Birkmayer and Schindl tried to determine whether Magnus and de Kleyn's positional reflexes can be demonstrated in normal persons while skiing. Active rotation of the head to the left, with the eyes open or closed, produces deviation

of the course taken by the skier to the right. If the head is turned to the left while the eyes are maintained in a right lateral position, the course again deviates to the side opposite that of the rotation of the head. Lateral ocular movements with the head and neck fixed by plaster of paris have no influence. Inclination of the head to the right shoulder produces deviation to the same side. If rotation of the head to the right is combined with inclination to the right, deviation to the left occurs. When the angle of the slope suddenly increases, normal skiers prevent falling backward by bending their head and upper part of the body forward. This corrective movement is retarded or omitted if the peripheral part of the visual field is restricted by tubes placed in front of the eyes.

SPIEGEL, Philadelphia.

Diseases of the Brain

INTRACEREBRAL CARCINOMATOUS METASTASES. CLARENCE C. HARE and GABRIEL A. SCHWARZ, Arch. Int. Med. **64**:542 (Sept.) 1939.

Hare and Schwarz review the intracerebral metastases in 100 cases. Carcinomas may metastasize to the central nervous system (1) by direct extension, as in the case of carcinoma of the nasopharynx, (2) through the lymphatic structures and (3) via the blood stream, as carcinomatous emboli. The last type is the most frequent. In this paper Hare and Schwarz consider mainly diffuse metastatic cerebral disease. The clinical diagnosis of cerebral metastasis is relatively simple when the patient is known to have a primary neoplasm elsewhere. When the signs of a primary tumor are lacking, diagnosis may be difficult or established only by craniotomy and subsequent search for the primary focus. In many cases the correct diagnosis is established only at autopsy. The most frequent incorrect clinical diagnoses are: primary cerebral tumor, vascular accident, abscess of the brain, encephalitis, psychoneurosis or psychosis.

The frequency of metastatic intracerebral tumors varies with different published series. Cerebral metastases in cases of malignant disease vary from 18 to 31.2 per cent. The authors estimate the average incidence of metastatic cerebral tumors in their series to be between 10 and 20 per cent. In their cases the distribution of origin was as follows: In 42 per cent the primary site was the bronchus, and in 23 per cent, the breast; in 16 per cent the site was undetermined, while in the remaining cases the primary sources were scattered. The age of the patients varied from 12 to 30 years, with the greatest incidence in the third, fourth and fifth decades of life. There were 54 males and 46 females. The symptoms varied in duration from one week to eighteen months, but in 84 per cent of the cases symptoms were present less than five months. The onset in 36 per cent of the cases was sudden—convulsions, headaches, vomiting and hemiplegia being the most prominent disturbances. The symptoms in 42 cases developed gradually. Headache was the outstanding symptom in this group, with mental disturbance the next most frequent. In 17 cases the symptoms developed slowly, with headache again the outstanding symptom. In cases in which the onset was relatively rapid the symptoms often simulated closely those occurring in a cerebrovascular accident. Forty of the patients appeared well nourished; 29 had pronounced cachexia, and 31 complained of weakness, fatigue and loss of weight. Headache of varying degree was the outstanding symptom in 83 cases, while vomiting occurred at some stage of the illness in 59. In 49 per cent of the cases papilledema developed. There were mental disturbances of various degrees, consisting of retardation, irritability, defect of memory and profound confusional states. Convulsions, either focal or generalized, developed in 20 cases. Clinical evidence of destruction or direct compression of cerebral tissue was present in 68 cases. Some disturbance of the pyramidal tracts was observed in 35 cases. Aphasia, ataxia, local sensory disturbance and hemianopia were next in frequency. The physical signs, in general, were well marked, and once they developed there was no improvement. Many patients had more than one of the aforementioned signs.

The cerebrospinal fluid was studied in 54 cases; in 38 there was some abnormality of the protein value, and in a few a cellular response was evidenced. In 2 of 18 cases the spinal fluid pressure was elevated. Stereoscopic roentgenograms were made in 91 cases, 51 of which were abnormal. Metastasis to the bones of the skull occurred in 15 cases, displaced the pineal gland in 24 cases and caused erosion of the sella or the posterior clinoid processes in 22 cases. Encephalograms indicated neoplasm in 8 of the 10 cases investigated. Ventriculograms made in 9 cases were all abnormal, but only 3 gave evidence of definite localizing value. The diagnosis was simple in cases in which a known primary carcinoma was followed by signs of a cerebral neoplasm. The majority of the incorrect diagnoses were made in cases of primary tumors of the lung, in which the patients were thought to have a primary cerebral neoplasm.

Pathologic studies were made in 34 cases, in 20 of which there were multiple tumors. The tumors were usually observed at the junction between the central white and the cortical gray matter. This site is also the usual location for metastatic cerebral abscesses, and it was suggested that the lesions occur in this region because the pial arteries branch into their terminal capillaries at this point. The size of the tumors varied from that of a pinhead to a diameter of 10 cm. In a majority of cases the cell types in the metastatic tumors were identical with those of the primary growth. In a few cases tumor cells were observed within the lumen of the blood vessel, and at the margin of larger tumor nodules small clumps of tumor cells were seen invading the nearby parenchyma about the blood vessels. The brain tissue in an involved area was largely destroyed and replaced by tumor, which is one explanation of the infrequent presence of increased intracranial pressure.

BECK, Buffalo.

PROLONGED HYPERTHERMIA. WARD J. MACNEAL, HENRY H. RITTER and S. MILTON RABSON, Arch. Int. Med. **64**:809 (Oct.) 1939.

The authors report a case of hyperthermia in a nurse who had a finger amputated because of an infection. Subsequently, there developed signs of cerebellar involvement due to invasion of the blood stream by Staphylococcus aureus. After bacteriophage therapy the blood culture became sterile, but the patient had a high temperature. This suggested localization in the central nervous system. At autopsy there were observed edema of the cerebral cortex, congestion and extravasations of blood in the basal ganglia and an irregular, ragged cavity in the cerebellum. Unfortunately, the patient was not tested with multiple thermometers, and the clinical observations were not critically exact.

BECK, Buffalo.

STUDIES ON "ESSENTIAL" HYPERTENSION. HENRY A. SCHROEDER and J. MURRAY STEELE, Arch. Int. Med. **64**:927 (Nov.) 1939.

Schroeder and Steele analyzed 218 cases of "essential" hypertension. All the patients had been referred as having typical essential hypertension, and either exhibited or had exhibited elevation of diastolic pressure without evidence of failure of renal function. The cases were divided into five main groups on the basis of the following etiologic factors: renal disease, disorders of the central nervous system, endocrine dysfunction, vascular disease and unclassified disorders. In the group of diseases of the central nervous system, the following symptoms were noted: (1) vasomotor instability, (2) emotional instability, (3) autonomic instability and (4) arterial hypertension. These symptoms were usually found in young women who had had conflicts. In addition, there were included cases in which there were diencephalic attacks, consisting of irregular, blotchy blushing of the face and abdomen, spontaneous watering of the eyes, excessive perspiration, rise in blood pressure and coldness of the extremities. Changes in the retina and cardiac and renal failure were unusual in the cases of essential hypertension of nervous origin.

BECK, Buffalo.

PROLONGED CHOREA. L. BABONNEIX and P. GUILLY, Rev. neurol. **72**:149, 1939.

Sydenham's chorea rarely lasts longer than three or four months. The disease may be regarded as prolonged if choreic movements continue without remission beyond this period. In many cases reported in the past as instances of prolonged chorea the condition was not true chorea, for the movements were tics or were athetotic. Other cases concerned patients who had acute chorea, followed by a remission and the development of Huntington's chorea independent of the first attack of chorea. In still other cases there were symptoms of cerebral syphilis or of infantile dementia paralytica. When these cases are eliminated there remain few true cases of prolonged chorea. In all 3 cases observed personally by the authors, there were associated manifestations, leading to the probable etiologic diagnoses of epidemic encephalitis in 2 cases, and of multiple sclerosis or epidemic encephalitis in a third.

LIBER, New York.

PHYSIOPATHOLOGY OF THE FRONTAL LOBES. L. BARRAQUER, Rev. neurol. **72**: 160, 1939.

A girl aged 8 years had headache, vomiting, pallor of the optic disks, ataxia, muscular hypotonia, disorientation and left hemiparesis. Death followed craniotomy. Necropsy revealed an enormous sarcoma of the right frontal lobe. The cerebellum was intact. The hypotonia was of exclusively frontal origin. Walking in circles and disorientation in space are known results of lesions of the frontal lobe. In the case of a girl aged 14 suffering from a craniocerebral wound in the left frontal region, both of these symptoms were present. Craniotomy revealed several fragments of bone, as well as hair, embedded in the brain. The foreign bodies were removed and the patient recovered. These 2 cases are presented because of the undeniable lesions of the frontal lobe.

LIBER, New York.

PROBLEM OF MISLEADING SYMPTOMS ASSOCIATED WITH CEREBRAL TUMORS. E. PICHLER, Arch. f. Psychiat. **110**:75 (June) 1939.

Of 100 consecutive cases of cerebral tumor, the diagnosis and localization of which was proved at operation or autopsy, symptoms referable to the brian stem or the cranial nerves were manifested in 35. Far from being helpful in the localization of the lesion, these symptoms actually proved misleading in that they pointed to regions at a distance from the tumor. In 1 case there was diabetes mellitus, in 1 diabetes insipidus and in 1 a predominantly manic type of disturbance; these are explained by the author as being due to lesions of the hypophysial-diencephalic system caused by shifting of the brain stem laterally. In other cases similar diencephalic vegetative disturbances can be explained on the basis of ependymitis. In 5 other cases cerebral tumors were accompanied by homolateral hemiplegia. This seemed to have been caused by nicking of the contralateral peduncle by the tentorium, or by marked lateral displacement of the midbrain. In 1 case disturbance of the quadrigeminal plate was produced by changes in the configuration of the midbrain. Sometimes similar disturbances were produced by impingement of extensions from the tumor on the midbrain. In another case a lesion of the optic nerve was caused by a protrusion of the uncus. In 4 of the cases there were paralyses of the abducens nerve resulting from pressure, and in 8 cases Argyll Robertson pupils were present. Horner's syndrome was found in 3 cases. In 3 cases of tumors of the temporal lobe homolateral neuralgia of the fifth nerve occurred, and in another case this was bilateral. In 2 cases cerebral tumor was accompanied by symptoms referable to the pons.

MALAMUD, Worcester, Mass.

MULTIPLE HERNIATIONS OF THE BRAIN AS SEQUELAE OF CEREBRAL TUMORS. JOSEPH VON BALÓ, Arch. f. Psychiat. **110**:445 (Aug.) 1939.

Owing to mechanical interference, tumors of the brain may give rise to herniations of the cerebral cortex, varying from the size of a millet grain to that

of a pea; these make their way through the dura and impinge on the skull. They are observed most frequently on the inferior surface of the temporal and frontal lobes, near the interhemispheral fissure and in the occipital lobe. They are produced by increased intracranial pressure and are seen mostly in association with tumors, but they occur also with other disease processes accompanied by increased pressure. It is also possible that such herniations are found without increased pressure, but this question has not been settled. Sometimes they are present without clinical symptoms. The neurosurgeon, however, must always take them into account as a possibility, particularly in attempting to localize a lesion. Since these herniations may take place at the site of the pacchionian granulations, they may sometimes become of importance in the circulation of the cerebrospinal fluid within the cranium.

MALAMUD, Worcester, Mass.

MONOPLEGIA OF THE FINGERS AND TACTILE AGNOSIA. L. HALPERN, Schweiz. Arch. f. Neurol. u. Psychiat. **44**:35, 1939.

Halpern reports the case of a man aged 33 suffering from hypertension, who complained of headache when examined three months after he had had a massive intraocular hemorrhage. Objective neurologic findings at this time were limited to questionable weakness of the muscles about the right angle of the mouth. Four weeks later the right hand became weak, and loss of power was then discovered in all the digits, particularly the thumb and index finger, of this hand. Strength was normal at the wrist, but active extension of the fingers was impossible. Mayer's finger reflex could be demonstrated only on the uninvolved, or left, side. Although all modalities of superficial and deep sensation, including sense of position, were intact, the patient was unable to recognize by the sense of touch various objects which were placed in his right hand. The patellar and achilles reflexes were active on both sides; Oppenheim's reflex was present on the left, but Babinski's reflex could not be elicited on either side.

The second patient, a man aged 36, had complained for a time, eighteen months previously, of vertigo and a sticking sensation in the finger tips of his left hand. Two months before examination he had begun to have frequent sensations of numbness and tingling in the left hand and about the left corner of the mouth. He also had a feeling of heaviness in the head and difficulty in concentration. The left hand became weak a few days later, and at this time the patient was found to have polycythemia. The concentration of hemoglobin in the blood ranged from 125 to 140 per cent, and the number of erythrocytes varied between 6,750,000 and 7,170,000 per cubic millimeter. The muscles of the lower portion of the face seemed a trifle weak on the left side, and movements of the left wrist showed some loss of power, but the weakness was more pronounced in the extensor and adductor muscles of the fingers. Mayer's finger reflex was present only on the uninvolved, or right, side. Sensation was unimpaired, and the patient was able to recognize numbers which were traced on either hand. He could not, however, name articles which were placed in his left hand, although he was aware, when not too fatigued, of some of the surface qualities of the given objects. The gnostic sense was less involved in the thumb than in the remaining digits of the left hand. The abdominal and patellar reflexes were more active on the left, but no pathologic reflexes were elicited.

The monoplegia of the fingers and the associated tactile agnosia observed in both cases are believed to have resulted from thrombosis of the rolandic artery, which is the main source of blood supply to the anterior and posterior lips of the central fissure. According to Foix, the hemiplegias occasionally observed in cases of focal softening in the territory of the rolandic artery are accompanied by practically no sensory disturbances. Halpern believes, nevertheless, that occlusion of this artery alone could account for the combination of symptoms described in the cases he reports. Apparent limitation of softening to the middle portions of the precentral and postcentral gyri is explained on the basis of the rich collateral circulation in this region. Tactile agnosia is usually attributed to cortical

lesions of the postcentral gyrus and the contiguous parietal lobule. Pure astereognosis, which is generally accompanied by ataxia and disturbances of deep sensibility, on the other hand, is generally ascribed to lesions of the supramarginal gyrus. Foerster has reported 2 cases of circumscribed involvement of the sensory area for the fingers in the postcentral gyrus. One patient had pure tactile agnosia; the other had astereognosis in addition. Foerster expressed the view that tactile agnosia was due to destruction of the superficial layers of the postcentral cortex.

DANIELS, Denver.

Peripheral and Cranial Nerves

CONGENITAL DEFECTS OF THE CRANIAL NERVES: AN ASSOCIATED PORENCEPHALY AND AGENESIS OF THE CORPUS CALLOSUM DIAGNOSED BY VENTRICULOGRAPHY. D. L. REEVES, Bull. Los Angeles Neurol. Soc. **4**:184 (Dec.) 1939.

In the first case reported by Reeves, a girl aged 2 months, with a history of holding the breath, choking spells, cyanosis and hoarseness since birth, was found to have an elongated, edematous epiglottis, which caused laryngeal obstruction, pallor of both optic disks, ptosis of the right eyelid and a tendency for the right eye, but not the left, to close on crying ("jaw winking"). The child died of bronchopneumonia six weeks later; at autopsy examination of the brain was not permitted. In the second case a girl aged 6 months had had convulsions since the age of 2 months. Birth had been apparently normal. The child had never held up the head or sat alone. The head was acrobrachycephalic. There were a congenital coloboma of the left optic nerve and pigmentary degeneration of the retina. The pupils reacted sluggishly; the abdominal reflexes were absent, and a Babinski reaction was present on both sides. Lumbar puncture with the patient under medication showed a pressure of 375 mm. of spinal fluid. A ventriculogram revealed a large cavity in the midline connected with the lateral ventricles, the anterior horns of which were widely separated. The diagnosis was porencephaly with agenesis of the corpus callosum. If this diagnosis is subsequently verified, this case will represent the earliest age at which agenesis of the corpus callosum has yet been diagnosed ventriculographically.

MACKAY, Chicago.

TRIGEMINAL NEURALGIA IN MULTIPLE SCLEROSIS. BENJAMIN FINESILVER, J. Nerv. & Ment. Dis. **90**:757 (Dec.) 1939.

Finesilver reports 3 cases of multiple sclerosis in which the initial symptom consisted of paroxysmal pain in the area of distribution of the trigeminal nerve. In 1 case less severe pains also occurred in the lower extremities. Section of the sensory root gave permanent relief in 1 case, and two injections of alcohol in another case relieved the patient for a year on each occasion. No loss of sensibility was found in the trigeminal area in any of the cases. The clinical manifestations of multiple sclerosis were clearly marked and progressive in all 3 cases. Finesilver believes that the neuralgic pain in multiple sclerosis may be of peripheral or central origin, and that relief by section of the root indicates a peripheral lesion.

MACKAY, Chicago.

SO-CALLED LACTATION NEURITIS. M. GLEES, Klin. Monatsbl. f. Augenh. **103**:615 (Dec.) 1939.

Glees says that during the puerperium or shortly thereafter there may develop, accompanied by headaches, impairment of the visual acuity of one or both eyes. Examination discloses optic neuritis, peripheral contractions of the visual field and central scotomas. Occasionally the bulbs are sensitive to pressure, and the movements of the eyes may be painful. The disorder subsides in the course of weeks or months, and the visual acuity is largely restored. Thus the prognosis

is relatively favorable. The cause is unknown. Glees reports 3 cases of lactation neuritis observed at his clinic during 1938. In the first case the disorder developed eleven weeks after delivery and five weeks after the child had been weaned. In the second case it appeared four weeks, and in the third case six weeks, after delivery; both of the women were still nursing their infants when the ocular disorder developed. In all cases the disorder was characterized by severe changes in the papilla, and in 2 cases there existed vascular changes and retinal edema in the region of the papilla and along the large vessels. In view of the fact that vascular changes, particularly contraction of the arteries, have been observed by others who have studied lactation neuritis, the author concludes that vascular changes play a part in the pathogenesis of this type of optic neuritis. To be sure, this does not explain why they appear during the period of lactation. None of the hypotheses give a satisfactory explanation, and the author regards a direct connection between the disease of the optic nerve and lactation as doubtful. He accepts as most plausible the theory that weakening of the organism by gestation, delivery and the puerperium provide the basis for some infectious impairment of the optic nerve.

J. A. M. A.

Vegetative and Endocrine Systems

CHLORIDE EXCRETION IN HYPOPITUITARISM WITH REFERENCE TO ADRENOCORTICAL FUNCTION. D. J. STEPHENS, Am. J. M. Sc. **199**:67 (Jan.) 1940.

Stephens reports 7 cases of demonstrable lesions of the hypophysis, in 6 of which there was definite evidence of clinical hypopituitarism. A modification of the chloride depletion test recently described by Cutler, Power and Wilder (Concentrations of Chloride, Sodium and Potassium in Urine and Blood, *J. A. M. A.* **111**:117 [July 9] 1938) was used. Each of the 6 patients with hypopituitarism showed significant decreases in serum chloride during the period of chloride depletion and a high concentration of chlorides in the four hour specimen of urine collected at the beginning of the third day, characteristic of adrenocortical insufficiency. Four of these 6 patients showed symptoms suggestive of the addisonian crisis, associated with decrease in the serum chloride level, which were promptly relieved by the intravenous administration of sodium chloride, dextrose and extract of adrenal cortex. In 2 patients symptoms failed to occur and chloride excretion was favorably modified after the administration of sodium chloride and extract of adrenal cortex. The data are interpreted as confirmatory evidence of the occurrence of chronic adrenocortical insufficiency in clinical hypopituitarism, presumably secondary to withdrawal of the adrenotropic principle of the anterior lobe of the pituitary.

MICHAELS, Boston.

THE EFFECT OF ESTRIN [ESTROGEN] ON THE ANTERIOR PITUITARY OF MALE RATS AFTER PITUITARY STALK SECTION. U. U. UOTILA, Endocrinology **26**:123 (Jan.) 1940.

Uotila states that there is increasing evidence to indicate that the anterior lobe of the pituitary gland has a basic secretory ryhthm which is controlled humorally by the hormones of other endocrine glands. In this experiment he confirms the conclusion in the case of the effect of estrogen on the gonadotropic and corticotropic functions of the gland in male rats. Large doses of estrogen (daily injections of 20 rat units of estradiol benzoate), injected into male rats for twenty days, acted on the anterior lobe of the pituitary gland without the mediation or modifying effect of the pituitary stalk. This was evidenced by the following facts: (*a*) The anterior lobe of the pituitary gland underwent hypertrophy and showed the same cytologic changes in rats which had received estrogen whether the stalk was intact or severed; (*b*) estrogen suppressed to an equal extent the secretion of the gonadotropic principle in male rats in which the stalk had been cut and in those

in which it was intact, as shown by the appearance of marked atrophy of the testes and seminal vesicles in the two groups. The adrenals hypertrophied equally after treatment with estrogen in animals in which the stalk was intact and in those in which it had been sectioned, indicating that estrogen also affects the corticotropic function of the anterior lobe of the hypophysis without mediation or modification by the pituitary stalk. Uotila concludes that estrogen acts directly on the anterior lobe of the hypophysis, and that this action is a part of the humoral control of the basic secretory rhythm of the gland.

PALMER, Philadelphia.

PRECOCIOUS PUBERTY IN A BOY OF ONE YEAR. I. FRASER, Brit. J. Surg. **27**:521 (Jan.) 1940.

Fraser reports a case of extreme virilism in a boy of 12 months, presumably the youngest patient in any case on record. Precocity in bone development and dentition was noted. The value of the capon and colorimetric tests, as well as the ponceau-fuchsine stain, was demonstrated. The boy until the age of 6 months was normal, when the penis began to enlarge rapidly, the prostate became the size of a walnut and erections were almost constant. Masturbation took place frequently, pubic hair appeared and acne of puberty appeared on the face. The face became old for his age, the voice deep pitched, hands greatly enlarged and muscular development excessive; the appearance of the epiphyses was greatly in advance of his age, and body weight increased out of all proportions. He ate about three times the supply of food normally given a child of his age. Mentally he was retarded. He was unable to talk and rarely used the "mamma-baba" words expected of a child of 12 months. He seemed to have little affection except for food. From the age of 6 months he lost his cleanly habits as regards urine and feces. He became bad tempered and difficult to manage. The author does not claim that these changes had any direct connection with his increased virilism. Briefly, the boy's age was (1) 12 months by calendar, (2) 12 months by mental advancement, (3) 5 years by bone epiphyses, (4) 3 years by dentition, and (5) 18 years by sexual organs (penis and prostate, but not testicles). Biologic tests carried out on the urine revealed that the boy at 12 months of age was more virile than the average man. Abdominal exploration revealed a tumor the size of a golf ball above the right kidney. The rest of the abdominal contents felt normal. After considerable delay, the second operation was performed when the boy was 18 months old. A high kidney incision was made. The twelfth rib was retracted and the adrenal tumor delivered with much greater ease and less bleeding than was expected. The tumor was pyriform, with the apex apparently attached without a stem to the inferior vena cava. The child was back in bed in thirty minutes; he recovered well and took fluids ravenously. Suddenly, twenty hours later, he collapsed and died. Complete necropsy was performed, but no abnormality other than enlargement of the vesicle and prostate could be found.

J. A. M. A.

Muscular System

CONGENITAL FACIAL HEMIHYPERTROPHY ASSOCIATED WITH OCULAR ANOMALIES: REPORT OF TWO CASES. RIFAT GÖZBERK, Ann. d'ocul. **176**:624 (Aug.) 1939.

Gözberk reports 2 cases of congenital facial hemihypertrophy associated with ocular anomalies. In 1 case there was hypertrophy of the eyelids, the cheek, the wing of the nose, one side of the lips, the malar bone on the same side and the zygomatic arch, associated with enlargement of the orbital cavity. In the second case there were overdevelopment of the eyelids and the petrous portion of the temporal bone on the same side and enlargement of the orbital cavity.

BERENS, New York.

ELECTROCARDIOGRAPHIC FINDINGS IN PROGRESSIVE MUSCULAR DYSTROPHY. V. PUDDU and A. MUSSAFIA, Arch. d. mal. du cœur **32**:958 (Nov.-Dec.) 1939.

Following a review of the literature on electrocardiographic studies of progressive muscular dystrophy, Puddu and Mussafia describe their results in 33 cases. In 29 months there were the symptoms of the ordinary forms of progressive muscular dystrophy and in 4 the symptoms of myelopathic dystrophy (Charcot-Marie type). The disease varied in its evolutive phase, from the most benign to the most grave. In only 2 of the 33 cases were there symptoms of cardiac disorders; an attack of tachycardia of a paroxysmal character occurred in 1 case and rheumatic cardiopathy with mitral stenosis in another. The authors made electrocardiographic records in all the cases, often several times, with three peripheral and two thoracic leads. In summarizing the results of their electrocardiographic studies, they say that in 30 of the 33 cases the electrocardiograms were normal. In 1 case there were rhythmic disturbances. Repeated electrocardiographic tests disclosed abnormal tracings indicating that this was a typical case of the syndrome of Wolff, Parkinson and White. Only after intense questioning did the patient recall short attacks of palpitation. One patient had an abnormal P wave. This patient had a history of rheumatism; he had mitral stenosis, and the electrical axis was deviated to the right. In 1 case the PR interval was prolonged. Clinically the heart was normal and the anamnesis was negative. Several aspects which were observed in this series or reported in the literature, such as inversion of T_3 or a deep Q_3, are regarded as of no pathologic significance. The authors conclude that the electrocardiogram in cases of muscular dystrophy can be altered in subjects who have signs or clinical symptoms of cardiopathy. In general it does not bring to light any new fact that can be attributed to latent or hidden cardiac lesions. J. A. M. A.

GENERALIZED MUSCULAR HYPERTROPHY OF INFANT AND CONGENITAL HYPOTHYROIDISM. H. DARRÉ, P. MOLLARET, ZAGDOUN and OEHMICHEN, Rev. neurol. **72**:249, 1939.

A full term girl, weighing 3,000 Gm., presented regurgitation almost immediately after feeding and inadequate gain in weight. Changes in the feeding formula and in intervals of feeding produced no relief. The weight began to decline. Tenacious constipation set in. Examination at the age of 5 months revealed generalized muscular hypertrophy. In the head, the buccinator muscle and the tongue were particularly affected; in the upper extremities, the deltoid, biceps, brachioradial and, most of all, the thenar and hypothenar muscles; in the trunk, the pectorales, the rectus abdominis and the anal sphincter, and in the lower extremities, the quadriceps, the adductors, the gastrocnemius and the peronei laterales. No myotonic reactions were present, either to mechanical or electrical stimulation. Roentgenograms showed thickening of the wall of the stomach and distinct hypertrophy of the diaphragm and heart. Neurologic examination gave entirely negative results. The temperature was between 35 and 36 C. (95 and 96.8 F.). It rose to 37 (98.6 F.) only on the occasion of an intercurrent infection. The skin was of fine texture and easily creased. The panniculus adiposus was totally absent. Examination of the blood showed moderate anemia (2,700,000 red cells, 70 per cent hemoglobin). A tuberculin test gave negative results. Serologic tests for syphilis gave negative results in the blood and spinal fluid, which were also normal in other respects. Quantitative determinations of the dextrose, total lipid, cholesterol and calcium contents in the blood gave normal results. The region of the thyroid gland was normal to palpation. There was no evidence of rickets. Roentgenographic examination of the entire skeleton revealed absence of several epiphysial points of ossification which are normally present at birth. Biopsy of a muscle showed no hypertrophy, but actual slenderness of muscle fibers, together with increase in their number (hyperplasia), and zones of sclerosis. Treatment with thyroid for three months did not result in improvement. Two weeks after the end of this medication, gradual improvement of all the manifestations, including muscular hypertrophy, hypothermia, bradycardia, cardiomegaly and low voltage of

the ventricular complex, began and persisted to the time of writing, four months later. This case is concluded to be an example of the Debré-Semelaigne syndrome, first described by these authors *(Bull. Soc. de pédiat. de Paris;* **23**:542, 1934). It consists of generalized muscular hypertrophy, muscular rigidity, intellectual retardation and a myxedematous syndrome in babies. Improvement of all the manifestations follows administration of thyroid. The syndrome of C. de Lange, reported in the same year, consists of generalized muscular hypertrophy, hypertonia, interpreted as of extrapyramidal origin, and mental deficiency. No thyroid therapy was tried. Debré and Semelaigne claimed that the two syndromes are identical, while de Lange maintained their distinctness. Other cases reported in the literature have been interpreted as instances of infantile Thomsen's disease. In some of the latter thyroid therapy has been used with favorable results. The authors conclude that all these types of generalized muscular hypertrophy in infants are the Debré-Semelaigne syndrome, that true Thomsen's disease is thus far unknown in infants and that in all cases of infantile generalized muscular hypertrophy thyroid therapy should be used.

LIBER, New York.

Special Senses

RHINOGENOUS BITEMPORAL HEMIANOPIA IN THE COURSE OF RHINOGENOUS NEURITIS AND ITS PATHOGENESIS: REPORT OF A CASE. SAKAE KITAHARA, Ann. d'ocul. **176**:316 (April) 1939.

Clinical study of a case of rhinogenous bitemporal hemianopia revealed that inflammation of the surrounding cavities caused circumscribed inflammation or collateral edema of the dura mater close to the optic chiasm, and that the compression of the latter caused bitemporal hemianopia, unaccompanied by general or cranial symptoms.

BERENS, New York.

INVERSION OF THE FIELDS FOR COLOR ASSOCIATED WITH QUININE AMBLYOPIA. CONSTANTIN DRACONTAIDIS, Ann. d'ocul. **176**:437 (June) 1939.

The author reports 8 cases of quinine amblyopia in which inversion of the visual field for colors was noted. This change is due to the different threshold for excitation of the cones, which are in a state of hypofunction after the toxic action of quinine. Normally, for the perception of red, a physicochemical stimulant of slight intensity is necessary, while for perception of blue and green one of great intensity is required. Hypofunction of the rods and cones makes the latter less able to perform their normal functions, which consist in transforming their physicochemical process into nervous excitation through the action of light. This becomes especially evident when colored light is used, because the luminous rays of different wavelengths stimulate differently the sensitive retinal elements (rods and cones) and, consequently, produce a different reaction. The degree of degeneration of the rods and cones may be judged by the intensity of this reaction.

Although intense treatment was applied in the cases reported, there were no changes in the simple atrophy of the optic nerves, which was progressive and caused by the destruction of the ganglion cells of the retina. There was no enlargement of the visual field beyond a certain limit. Together with the treatment for poisoning (repeated lavages of the stomach), the author advises immediate administration of antispasmodic and diuretic remedies, such as amyl nitrite, acetylcholine and euphylline (a combination of theophylline and ethylenediamine), to improve the circulation of the retina and to render the organism capable of immediately rejecting the absorbed quinine.

BERENS, New York.

BINASAL HEMIANOPIA. JORGE MALBRAN, Ann. d'ocul. **176**:491 (June) 1939.

According to Malbran, cerebral tumor is the most frequent cause of binasal hemianopia. Binasal deficiency never begins with a binasal scotoma. The onset

is usually peripheral, occurs most often in the inferior quadrants and progresses slowly. A vascular mechanism is undoubtedly a factor. In order that compression by the anterior cerebral arteries may affect the direct fibers it must occur in the anterior part of the chiasm. This is possible only when the chiasm is located posteriorly or when the optic nerves are long. This condition is associated with tumors of the third ventricle. The dilatation of this ventricle is accompanied by papilledema. The frequency of papilledema in association with binasal hemianopia is thus explained. Any tumor producing dilatation of the ventricle and displacement of the brain may cause binasal hemianopia.

BERENS, New York.

TUBEROUS CEREBRAL SCLEROSIS WITH "PHACOMA RETINAE" OF VAN DER HOEVE: REPORT OF THREE CASES. M. ANKER and A. KVEIN, Ann. d'ocul. **176**:833 (Nov.) 1939.

Anker and Kvein describe in detail the ophthalmic lesions observed in 3 patients suffering from tuberous sclerosis. These were: a veiled papilla; white lines along the retinal vessels; white, strawberry-shaped tumors; small white foci, which were slightly prominent, and foci of ordinary atrophy of the choroid. These symptoms correspond with those described by van der Hoeve in 1921. He differentiated three types of tumors and suggested the term "phacoma" to designate them.

BERENS, New York.

EXOPHTHALMOS ASSOCIATED WITH INTRACRANIAL TUMORS. H. SKYDSGAARD, Ann. d'ocul. **176**:834 (Nov.) 1939.

Exophthalmos is in some cases the only symptom of an intracranial tumor. In a series of 352 cases of intracranial tumors, exophthalmos was present in 14 (4 per cent). These cases demonstrate that exophthalmos is associated with tumors of the middle and anterior fossae, particularly with meningiomas of the wing of the sphenoid bone. The clinical picture, in which exophthalmos is manifested, varies according to the importance of the other symptoms, such as changes in motility and stasis. The unilaterality of exophthalmos is also important, especially with respect to meningiomas of the wing of the sphenoid. The exophthalmos differs from that of exophthalmic goiter in that it seems to be due to massive expulsion of the orbital contents. Papilledema may or may not be present with the lesion. Exophthalmos does not seem to be related to intracranial hypertension. There is no indication that it is the result of sympathetic irritation.

BERENS, New York.

Diagnostic Methods

EVALUATION OF THE ELECTROENCEPHALOGRAMS OF SCHIZOPHRENIC PATIENTS. P. A. DAVIS, Am. J. Psychiat. **96**:851, 1940.

Davis studied the electroencephalograms of 132 schizophrenic patients, using the records of normal medical students as a base line. She found that records of the schizophrenic persons are divisible into three types: (1) Normal records. Patients with normal tracings had had a gradual onset of the illness; the family history of mental illness was less conspicuous, and they frequently suffered from the paranoid type of the disease. (2) Records of dysrhythmic pattern similar to that in epilepsy. Patients with this type constituted the largest group. The difference between the dysrhythmia of epilepsy and that of schizophrenia seemed to be one of degree. This group of patients were predominantly catatonic or had occasional catatonic episodes. (3) "Choppy" patterns suggesting an organic pathologic process. The disturbance was diffuse rather than focal. Patients with such records constituted the smallest group.

Pharmacologic treatment induced, or if already present increased, abnormalities of the electroencephalogram. Under total push therapy no change in the electroencephalogram was noted.

FORSTER, Boston.

ELECTROENCEPHALOGRAPHY IN THE PSYCHOSES. MORTON A. RUBIN, Am. J. Psychiat. **96**:861, 1940.

Rubin, working on the basis that an atrophied area of cortex should exhibit a type of alpha activity differing from that of the neighboring normal tissue, devised a method consisting of placing a double row of seven grounded electrodes so that three were over the frontal lobe, one was over the fissure of Rolando, one over the parietal lobe, one over the parieto-occipital fissure and another over the occipital lobe. Two meters each of filtered and unfiltered record was obtained, and from this the percentage of alpha waves, i. e., the quantitative amount of alpha rhythm, was deduced. The percentage of alpha rhythm in 2 meters of record was computed as the per cent time alpha. The author studied 9 schizophrenic patients by this method as well as by pneumoencephalography, 5 schizophrenic patients by this method alone and 2 patients with manic-depressive psychoses and 1 with a traumatic psychosis by both pneumoencephalographic and electroencephalograhic means. In the case of traumatic psychosis no alpha activity could be found. In 6 of the 11 other cases in which studies were used as controls there were dissimilarity of the distribution curves of the alpha rhythm and atrophy as revealed by air studies. In 4 no atrophy was apparent on air study and no changes were seen in the electroencephalogram. In 1 there were doubtful changes in the pneumoencephalogram but none in the electroencephalogram. Rubin concluded that the criterion for atrophy is the occurrence of marked differences in the change of slope of the plotted curves for the distribution of the alpha rhythm in the two hemispheres.

FORSTER, Boston.

VISUALIZATION OF CYSTIC CAVITIES IN CEREBRAL NEOPLASMS BY INJECTION OF THORIUM DIOXIDE. T. DE LEHOCZKY, J. belge de neurol. et de psychiat. **39**:715 (Nov.) 1939.

De Lehoczky reports the case of a man aged 48 with a tumor in the right temporal area which was diagnosed encephalographically. Amber fluid was obtained on puncture of the right temporal lobe. Two cubic centimeters of colloidal thorium dioxide was injected, and a nonencapsulated diffuse tumor was delineated roentgenologically. The patient died on the following day, before an operation could be performed; postmortem examination revealed a large glioblastoma multiforme occupying the major portion of the right temporal lobe. The author concludes that by injection of thorium dioxide into a cystic cerebral tumor the exact position and proportions of the lesion may be determined.

DE JONG, Ann Arbor, Mich.

Cerebellum and Brain Stem

A CLINICO-PATHOLOGIC STUDY OF PARENCHYMATOUS CORTICAL CEREBELLAR ATROPHY. RICHARD RICHTER, J. Nerv. & Ment. Dis. **91**:37 (Jan.) 1940.

Richter reports 3 cases of parenchymatous cortical cerebellar atrophy in siblings, with pathologic study in 1. In the first case a man began at the age of 47 to suffer from gradually increasing ataxia and shooting pains in the lower extremities. Examination at the age of 52 revealed: nystagmus; ataxia of the lower limbs; a positive Romberg sign; absence of the abdominal, reduction of the achilles and increase in the patellar reflexes; hypalgesia in the peroneal and ulnar areas and across the chest, and diminished vibratory sense at the ankles. Thereafter, the ataxia increased and involved the upper extremities. Writing

became impossible; speech was almost unintelligible. A year before his death, at the age of 65, he had occasional urinary incontinence and mental and visual impairment, with pallor of the optic disks and retinal arteriosclerosis. An older brother and a sister were unaffected, but an older sister and a younger brother exhibited similar disturbances.

Grossly, the brain revealed arteriosclerosis, slight atrophy of the frontal convolutions, moderate ventricular enlargement and diffuse, symmetric reduction in the size of the cerebellum and brain stem. Microscopically, about nine tenths of the Purkinje cells had disappeared, most of the remainder showing chromatolysis, swelling and deformity. Loss of the Purkinje cells was generalized, but more marked in the central, posterosuperior and lunate lobules. The molecular layer was reduced one fourth in width and the Lannois-Paviot glial layer stood out strikingly. There were numerous empty baskets; no loss of axis-cylinders or myelin was noted, but there was some decrease of the radial fibers of the cortex and the intragranular, infragranular, and supragranular plexuses. The ganglion cells of the dentate nucleus were decreased in number, with moderate degenerative changes in the remaining cells and some increase of the surrounding glia. The brain stem and medulla oblongata were normal, including the cerebellar peduncles, the internal and external arcuate fibers, the medial leminscus, the posterior longitudinal bundle, the gray pontile masses, the transverse pontile fibers and the inferior olives with their connections.

In the second case, almost identical clinical features were seen in the sister, who was first affected at the age of 47 and died with additional mental symptoms of senility at the age of 57. Her three daughters were normal at the ages of 42, 36 and 31, respectively. In the third case, a younger brother began to suffer from gradually increasing ataxia at the age of 55, and at 61 found a cane necessary in walking. His arms had not become affected. His two daughters, in the second decade of life, were normal.

Richter states that the pathologic changes in his first case differ from those reported by others only only in the lack of relative accentuation of the process in the superomedial portion of the cerebellum and in the rather marked changes in the dentate nucleus. In his opinion, the familial incidence, already noted by Thorpe in a previous case, makes an exogenous cause unlikely and suggests, rather, a genetic factor.

MACKAY, Chicago.

Congenital Anomalies

ANODONTIA IN MONGOLISM. D. H. H. THOMAS, J. Ment. Sc. **85**:566 (May) 1939.

Anodontia, the complete absence of teeth, both milk and permanent, is a rare condition. Thomas reports the case of a female mongolian idiot aged 61 who had complete anodontia of both the first and the second dentition. Thomas points out that both anodontia and mongolism are due to a developmental defect in the ectoderm, and that possibly both appear in the same period of ontogenetic development.

KASANIN, San Francisco.

OPERATIVE TREATMENT OF CONGENITAL CEREBRAL HERNIA. N. I. SOKOLOV, Vestnik khir. **57**:593 (June) 1939.

Sokolov has reviewed all cases of congenital encephalocele reported by Russian surgeons. Of the 143 patients, 119 underwent an operation; of these, 43 died, the mortality rate being 36.1 per cent. Of the 107 patients with frontal ethmoid encephalocele, 36 (33.6 per cent) died; in 3 (2.8 per cent) the results seem doubtful. Recovery was obtained in 68 (63.6 per cent). The author reports 8 cases observed by himself and offers his own plastic technic for hernia. His conclusions are as follows: 1. Frontal ethmoid encephalocele is the most common type in the soviet republic, the occipital variety being rare. 2. Infants with frontal ethmoid cerebral hernia display remarkable viability. 3. Infants with cystic encephalocele should be

operated on at the earliest possible time, even during the first days of life. In doubtful cases treatment may be postponed till the infant is a month old, but it should always be performed in the first year of life. 4. In cases of considerable bony defect the symptoms may seem grave, but they disappear after the plastic closure of the defect. 5. The inner opening of the bony canal in cases of nasofrontal hernia has unequal axes, the transverse axis usually exceeding the others; this is especially true in nasoethmoid hernia. The shape of the inner opening of the bony canal approaches an oval, the edges being fairly even. 6. The author recommends a one stage, external operation, the procedure for posterior orbital hernia being an exception to the rule. 7. In cases of nasoethmoid and nasofrontal encephalocele the closure of the inner opening of the canal with a bony graft inserted from the inside of the skull insures good results. The access to the inner opening is gained by means of mobilizing the anterosuperior and partly the lateral walls of the bony canal. A graft of a size exceeding that of the defect and completely covering it can be introduced into the cranial cavity without any difficulty, for which purpose the difference in the axes of the canal is made use of. 8. In the anterior orbital hernia the short narrow canal should be completely eliminated by the introduction of a pinlike cartilaginous graft. 9. The author believes a free bony autoplastic graft to be the best material for the closure of large defects in cases of encephalocele, the cartilaginous autoplastic graft being the best for smaller defects.

J. A. M. A.

Society Transactions

ILLINOIS PSYCHIATRIC SOCIETY

H. Douglas Singer, M.D., *President, in the Chair*

Regular Meeting, Feb. 1, 1940

Psychiatric Problems in a Clinic for Convulsive Disorders. Dr. Theodore T. Stone and Dr. Alex J. Arieff, Chicago.

This study includes all psychiatric aberrations observed in a group of 350 patients, exclusive of the feebleminded and deteriorated patients, who were institutional problems. In 1 case there was an idiosyncrasy to bromides even in small doses, which resulted in a confusional psychosis. The psychosis disappeared when the bromide medication was discontinued. In 5 cases mental aberrations occurred only in the course of an alcoholic spree, and then there were no seizures. The mental symptoms present were similar to those observed in nonepileptic persons who became intoxicated. In 2 cases mental aberration followed the onset of multiple seizures or status epilepticus. In 3 cases mental abnormality occurred during psychic or epileptic equivalents. There was 1 case of meningovascular syphilis. In 6 cases mental abnormalities complicated organic disease of the brain, namely, encephalitides, birth trauma, tumor of the brain, tuberous sclerosis and trauma to the head. In 1 case mental aberration was associated with a schizophrenic makeup. There were 3 cases of reactive depression; 2 of the patients committed suicide. In 1 case a hysterical makeup and an environmental problem were involved. In 1 case there was a psychopathic personality, and in 1 case, an unclassified psychosis occurring in a woman aged 46, who remains delusional despite the fact that she has only an occasional seizure.

At the outset it may be stated that the peculiar quirk or mental habitus said to be associated with epilepsy was found in only 1 case in the entire group. This indicates to us that the concept of a specific epileptic personality is overemphasized. It is admitted without reservation that the person suffering from a convulsive state may have some form of psychiatric aberration, but not that the mental aberration is directly related to the convulsive state. There may, and do, occur psychiatric manifestations during the interparoxysmal period in patients suffering from epilepsy. These mental abnormalities have their specific cause, and must not be dismissed by saying that they are part of the epilepsy. In our study of 26 cases in which psychiatric disorders occurred, there were only 7 in which the mental abnormalities could be said to be related to the convulsive state. In the other 19 cases the mental disturbance was foreign to or distinct from the epilepsy. These psychiatric aberrations may be of many types, varying from simple misunderstandings to severe psychotic episodes. It is essential that all persons with convulsive disorders who present mental aberrations be studied in detail in order to determine the cause. The severely psychotic person is better managed in a suitable hospital or a sanatorium. This is especially true of those with mental depressions. The less severely psychotic patient may be managed in the clinic as an ambulatory problem. Alcoholic debauches often occur in patients with convulsive disorders, chiefly because of difficulties at home and erroneous ideas regarding the nature of the seizures. In our group there were 5 patients who went on alcoholic sprees without knowing that their convulsive difficulty could be arrested or considerably improved by proper medication and abstinence from alcohol. In order to prevent multiple seizures or the status following an alcoholic escapade, it may become necessary temporarily to increase the bromide

medication. This increase should be dependent on frequent determinations of the bromide content of the blood stream. Any patient showing a severe idiosyncrasy to bromides or phenobarbital should either have such drugs withheld entirely or be given small doses in increasing amounts. It was thought that dilantin sodium might be of assistance in cases of this type, and it is being tried at present. All psychoneurotic behavior can be managed in the clinic. Explanation, encouragement, persuasion, rehabilitation and removal to foster homes are excellent aids.

Seventeen of the group of 26 patients are ambulatory, receive treatment and carry on a modified normal life. It is our opinion that there is needed a better understanding between the patient with controlled epilepsy and his employer.

DISCUSSION

Dr. Francis Gerty, Chicago: I always feel at a disadvantage in attempting to discuss epilepsy, because I know so little about it. What is called epilepsy is symptomatic of something. What that something is with respect to the idiopathic form has not been discovered. That being the case, one is limited in discussing epilepsy to a description of what the patient's behavior has been and what reactions he has shown.

I am somewhat astonished that the incidence of mental disorder was as low as 8 or 9 per cent in this series. Perhaps this is because my own experience is chiefly with the psychotic types. All the mental symptoms which have been mentioned have come under my observation at the Psychopathic Hospital. I see some patients in office practice, however, whose conditions may perhaps correspond to those described. They manage to work and yet have seizures. Some of them are in unusual occupations. For a number of years I had a patient who was a lineman for an electric light company. This man had major seizures, but never while on a pole. However, he finally lost his position because it became known that he had seizures elsewhere. Most people accepted this man as normal; nevertheless, he had decided emotional reactions, due to the fact that he knew he had epilepsy, although he was sure no seizure would ever occur while he was engaged in his occupation. Others work as salesmen. I am sure, nevertheless, that the very fact that they have epileptic seizures puts an emotional and mental burden on such patients.

Dr. Victor E. Gonda, Chicago: I wish to mention the case of a patient now under observation. A white man aged 26 suffered for twelve years from "idiopathic" epilepsy; after being struck on the head, status epilepticus developed and ended in a psychotic episode, during which he became so violent that he had to be restrained. He recovered. A few months later he had another accident; he had sexual intercourse with a Negro girl, and this fact worried him so much that gradually severe psychotic manifestations developed to the degree that he had to be admitted to the Psychopathic Hospital. He recovered. The third attack was two months ago, when he was notified that his elderly parents were divorced. During all three attacks his temperature rose above 106 F. Each time from 40 to 50 cc. of spinal fluid was removed. After the last episode of status epilepticus he did not show mental symptoms, but he lost all deep reflexes for seven days. They gradually reappeared; at first the reflexes of the upper, and then those of the lower, extremities could be elicited.

Dr. Roy Grinker, Chicago: My attention was directed to the 2 cases in which patients with epilepsy had depression and committed suicide. I am not facetious when I ask if the authors have any opinion regarding this phenomenon, in view of the fact that hundreds of patients with psychoses are being hospitalized for the production of fits to cure their depressions. As I look back on my own experience with epilepsy, I cannot recall any epileptic patient who has had a depression of such depth as to result in suicide.

I also wish to add my word to that of Dr. Gerty in considering the problem of the low incidence of mental disturbance associated with epilepsy. It is extremely low, much lower I think than is ordinarily experienced in private practice, but

especially low if one neglects, as I think one should not, the possibility that many epileptic patients may be having attacks as part of a psychologic process. I wonder whether the technic available in a clinic, where only casual interviews and superficial contact are possible, can be sufficiently detailed to have enabled the authors to determine the more subtle mental disturbances. Can they state, with any degree of certainty, that these attacks in themselves were not manifestations of certain psychologic processes?

DR. JOSEPH C. RHEINGOLD, Chicago: I wish to ask whether the authors observed alternation between the convulsive phenomena and the personality disorders. Within the last two months I have observed 2 cases in which such an alternation occurred, a period of seizures being accompanied by normal behavior and a period without seizures by aggressive, and in 1 instance almost maniacal, behavior.

DR. L. MEDUNA, Chicago: Development of schizophrenic states during administration of bromides to patients with epilepsy has been well known for about fifty years. This change in the disease was considered as a symptom of bromide poisoning. However, in many cases the bromide content of the blood is not high enough to justify speaking of poisoning, so one may assume that the appearance of the schizophrenic state is due not to bromide poisoning but to abolishing the epileptic attacks. The epileptic attacks in cases of schizophrenia or in those of combined schizophrenia and epilepsy may be considered as defense reactions of the organism against schizophrenia.

DR. THEODORE T. STONE, Chicago: I do not think we suggested that epilepsy is a specific disease. Every physician treats patients who have paroxysmal attacks of unconsciousness associated with a typical chain of symptoms. When one examines them, one does not find any organic signs. These patients may be lawyers, bankers, truck drivers or laborers. At present, no one knows why a patient has paroxysmal attacks of loss of consciousness with or without convulsions or psychic equivalents. It is known, however, that he has attacks because of a lowered threshold in the brain. Perhaps one is at fault for calling this disease an idiopathic convulsive state, but one must have a name for it. The term "idiopathic" can be used. It is a textbook word, meaning that no cause has been found.

With reference to the observation by Dr. Gerty concerning a telegraph lineman who had never had a convulsion while working on a pole, it may be said that this is a common observation. Many physicians who, unfortunately, had epilepsy up to the time they sought relief have performed operations and have had practically no seizures while they were operating. At the Passavant Hospital, my associates and I have found that when patients who have had seizures every day or every other day were hospitalized complete arrest of all attacks occurred. We do not know why this takes place.

We have not attempted to discuss the psychologic aspect of patients with the convulsive state. We hope to do that some day. Dr. Grinker mentioned that he had not observed any patient with the ordinary convulsive state who had a mental depression deep enough to produce an attempt at suicide. I cannot argue that. The 2 patients mentioned wrote notes saying that they were tired and discouraged, and then committed suicide. Such a condition we call reactive depression with suicide.

Dr. Rheingold asked about the periodic seizures: a period of seizures with normal behavior and a period without seizures with abnormal behavior. In our series we have had only 2 instances in which there were, between attacks, what has been described as a peculiar quirk or mental habitus characteristic of epilepsy. We have been amazed in this study at the type and infrequency of mental aberrations that have been found. The incidence is very low, and we are glad of that. We propose to continue to look for this particular type of mental disturbance.

Dr. Meduna asked whether the schizophrenic state occurred in patients who were being treated for the convulsive state with sodium bromide. In the cases of reactive depression and schizophrenia in our experience, we do not feel, so far

as we can judge, that the bromide or phenobarbital was responsible for such a reaction. It may be that the reaction is that of schizophrenia or a manic-depressive psychosis, but we have not drawn conclusions. Some one mentioned that it does not matter how much bromide one gives to patients, for most of them are sensitive to it. Many of our patients have a bromide content of the blood of 200 mg. but show no reaction, such as trembling of the hands or cutaneous eruption. Then, again, we have seen patients given 15 grains (0.975 Gm.) of bromides three times a day who on the second day showed mania or an acute cutaneous eruption. This indicates sensitivity to the drug, and because of that sensitivity the medication is discontinued.

The point we have tried to make is that there are certain types of patients with paroxysmal convulsive states who do not show any evidence of organic disease. Why is it possible for a peculiar mental reaction to develop out of a clear sky in such cases? We are trying to say that these patients, who are not institutionalized and are not deteriorated, may at times show paroxysmal mental symptoms, which may be alleviated. Further, these mental abnormalities are not due or related to the convulsive state.

Dr. Alex J. Arieff, Chicago: Among the cases in this series we have had 1 instance of real idiosyncrasy to bromides. The patient in this case had a bromide content of the blood of 140 mg. per hundred cubic centimeters, which the literature cites as a toxic level, but he probably would have had the same reaction with any dose. The cutaneous eruption has nothing to do with sensitivity to bromides. Acneiform dermatitis can occur with one dose, but it has nothing to do with the actual toxicity or the idiosyncrasy of the nervous system.

Electroencephalographic Study in a Case of Convulsive Disorder. Dr. Theodore J. Case, Chicago.

This article will be published in the *Illinois Medical Journal.*

Convulsions in Children Associated with Marked Disturbances in Behavior. Dr. Sam I. Stein, Chicago.

This article will appear in full in a later issue of the Archives.

Metrazol as a Diagnostic Aid in Cases of Epilepsy. Dr. H. H. Goldstein and Dr. Jack Weinberg, Chicago.

A comparative study by Jans of methods of diagnosing epilepsy revealed that the water retention test was a definite aid and that other tests were less reliable. In recent years much has been written on the applicability of an intravenous injection of metrazol to the diagnosis of epilepsy. In most instances this test has proved unreliable. We used subcutaneous injection of a 10 per cent solution of metrazol in doses of 5 cc. per hundred pounds (45.4 Kg.) of body weight. Of 84 schizophrenic patients, 1 had a grand mal seizure with this method, and it was questionable whether this patient had true schizophrenia. In 16, or 47.05 per cent, of 34 patients with idiopathic epilepsy the same method of administration of metrazol produced seizures. All seizures occurred within ninety minutes of the time of injection. We believe that this method is equal, if not superior, to the McQuarrie water retention test.

DISCUSSION

Dr. Ernst Gellhorn, Chicago: In connection with the work presented, I wish to mention that at the same time an attempt was made to measure quantitatively sympathetic excitability in schizophrenic and in epileptic patients. It was thought that the rise in blood sugar resulting from a given subconvulsive dose of metrazol might be an indicator of the excitability of the sympathetic nervous system. Since the measurement of the excitability of autonomic centers in schizophrenia

seems to be one of the most pressing problems, one should have knowledge of the excitability of these centers in various phases of the disease. In these investigations, in which Dr. Goldstein, Dr. Weinberg and I collaborated, 78 female patients with schizophrenia were given subcutaneous injections of 5 cc. of a 10 per cent solution of metrazol per hundred pounds of body weight. The average rise in blood sugar amounted to 9.2 per cent. Of the 23 female patients with epilepsy given the same amount of metrazol, 13 had no convulsions, and in this group the average rise in blood sugar was 18 per cent. These differences seemed significant, but, unfortunately, when we extended our work to the male epileptic patients we did not find a reaction which differed from that observed in the schizophrenic patients. Sixteen male epileptic patients who did not have convulsions showed a rise in blood sugar of 10 per cent after metrazol. These experiments, therefore, were not conclusive. Their brief presentation, however, may be justified in view of similar attempts which may be made by other investigators.

Dr. Julius I. Steinfeld, Des Plaines, Ill.: I am interested to know whether the number of seizures increased after injection of metrazol. I ask this for the following reason: A patient with a manic-depressive psychosis was treated in November 1938 by induction of a few metrazol convulsions. About Christmas 1938, approximately two weeks after treatment was completed, the patient, in some excitement, reported that while hunting during the holidays he became dizzy, lost consciousness and showed signs of a typical epileptic seizure. A few weeks later the same thing happened; there were also a number of petit mal attacks, in which he became dizzy and absentminded for a few seconds. The question arose whether the patient's condition was caused by the metrazol convulsions. On studying the history again, I found that at the age of 6 years he had had a fainting spell and at the age of 14 loss of consciousness, with asphyxia. He could not remember whether jerkings, cramps or biting of the tongue occurred with these seizures. Between the ages of 14 and 26 loss of consciousness had not occurred, and it was after treatment that he first reported the appearance of a definite epileptic seizure. It may be that the metrazol seizure lowered the convulsive threshold and caused the appearance of an epileptic seizure. He is now taking phenobarbital and is doing well.

Dr. Meduna, when I told him of this case, said that 2 similar experiences were reported to him.

Dr. L. Meduna, Chicago: The question of diagnosis by means of metrazol has been studied in Germany for about four years. I recently had a semiofficial letter asking if it would be possible, on the basis of the observations after administration of metrazol, to sterilize the patients who responded with a fit to a low dose of the drug. My first idea was that epileptic patients treated for years with bromides and phenobarbital are not to be compared with schizophrenic patients who have not been treated in the same way. I selected a number of schizophrenic and epileptic patients. To the epileptic patients I gave 3 grains (0.195 Gm.), and to the schizophrenic patients the same amount.

The previous treatment of schizophrenic patients is important, because metrazol is a potent drug. I found in my cases that every schizophrenic patient, without exception, responded with epileptic seizures after the administration of metrazol. The striking difference between the reactions of the two types was that schizophrenic patients reacted without exception to a dose above 5 cc. of a 10 per cent solution. The epileptic patients reacted to a dose of less than that amount. Another interesting feature of the metrazol test in cases of epilepsy is that if there is a focus the metrazol attack imitates the patient's original attack. In 2 cases in which the patient had been in a cloudy state for two weeks after a metrazol attack, the mental state became clear.

My final conclusion was that only in cases in which the results of the test are in accordance with other symptoms could they be used as a deciding factor.

Dr. Isidore Finkelman, Chicago: I wish to ask what the kymographic tracings of the motor pattern showed. Some tracings I have taken from schizo-

phrenic patients showed the typical tonic-clonic-tonic motor pattern. In the epileptic patient I have not seen any patterns of that nature. This point is of great importance in making a diagnosis of epilepsy.

Dr. Jack Weinberg, Chicago: First, I may mention that we are engaged in evaluating the various types of tests as diagnostic aids. We shall compare the results obtained in water retention tests, freezing the radial arteries and other methods with those which we have presented here. Possibly some patients who do not respond to one provocative test may to another.

Dr. Steinfeld asked whether the seizures increased in number after injections of metrazol. All the patients in our wards have been carefully checked before and after the test and we have not observed any increase.

I wish to thank Dr. Meduna for his comments. There are various reports on the results of intravenous injection of metrazol. The dose usually given was low in provocative tests. However, the method has proved unreliable. Only recently, 4 schizophrenic patients, concerning 1 of whom there was a question of epilepsy, were given metrazol. All were given 2 cc.; 3 had convulsive reactions; only the patient in whose case there was a question of epilepsy failed to respond. The higher doses reported, from 3 to 6 cc., may produce convulsions even in non-epileptic persons.

May I say that in the experiment to which Dr. Gellhorn referred all the female patients had been without medication for a month and the male patients for about a week? We did not obtain electroencephalograms for these patients.

In reply to Dr. Finkelman: We have not noted any difference between the convulsive patterns of the epileptic and those of the schizophrenic patients. All patients, whether schizophrenic or epileptic, showed clinic-tonic-clonic patterns. We watched them carefully because of our method of restraint, which compelled us to be close to the patients during the seizures.

As to the latent period, which we should have mentioned in our paper, 60 per cent of the patients responded within half an hour, 30 per cent in from half an hour to an hour, and 10 per cent in from an hour to an hour and a half.

PHILADELPHIA PSYCHIATRIC SOCIETY

Lauren H. Smith, M.D., *President, in the Chair*

Regular Meeting, March 8, 1940

Insulin Shock Treatment: Case of Death Due to Pulmonary Gangrene.
Dr. William Furst, Norristown, Pa. (by invitation).

A case is presented in which pulmonary edema occurred during insulin hypoglycemic coma and ended in death five days later, in spite of active treatment. At autopsy, incision into the right pleural cavity released foul-smelling gas suggestive of hydrogen sulfide. There was a marked fibrinous pleural reaction, with about 500 cc. of purulent yellow fluid in the pleural cavity. The entire right lung had undergone compression atelectasis, and the lower lobe presented marked bronchiectasis, with multiple areas of beginning abscess formation and gangrene. The other organs, including the brain, were essentially normal except for the associated toxic changes.

Nielsen and his associates (Nielsen, J. M.; Ingham, S. D., and Von Hagen, K. O.: Pulmonary Edema and Embolism as Complications of Insulin Shock in Treatment of Schizophrenia, *J. A. M. A.* **111**:2455 [Dec. 31] 1938) observed 3 patients with acute pulmonary edema during insulin shock therapy, but did not suggest a possible pathogenesis. Parhon and his co-workers (*Endocrinol., ginec., obst.* **3**:105 [Sept.] 1938) reported the occurrence of acute pulmonary edema in a schizophrenic patient during hypoglycemic coma. They expressed the belief that the condition followed the injection of epinephrine. Giordano and Zeglio (*Ztschr.*

f. klin. Med. **135**:212, 1938) showed that in normal fasting subjects the epinephrine content of the blood increases from 32 to 512 per cent after intravenous injection of 14 units of insulin. It is probable that, in an effort to maintain the body homeostasis, the sympathetic nervous system is stimulated after the injection of increasingly large doses of insulin. An excess of epinephrine is poured into the blood stream in order to maintain the level of the blood sugar. Termination of coma by administration of dextrose probably leaves an excess of circulating epinephrine. A rapidly increasing epinephrine level in the blood following termination of coma has been demonstrated by Heilbrunn and Liebert (*Endocrinology* **25**:354 [Sept.] 1939).

According to Bayer (Anatomy and Physiology of the Suprarenal Glands, in Piersol, G. M.: The Cyclopedia of Medicine, revised edition, Philadelphia, F. A. Davis Company, 1939, vol. 1, p. 165), hyperepinephrinemia results in diminished volume output and subsequent dilatation of the heart, especially of the left half. The enormously increased consumption of oxygen by the heart resulting from the intake of epinephrine can, notwithstanding the dilatation of the coronary vessels, be only partially compensated (Gremels). Overfilling of the left ventricle and auricle with blood may lead to acute pulmonary congestion and acute pulmonary edema, the latter of which constitutes the precursor of death in acute epinephrine poisoning.

It appears, therefore, that injection of epinephrine during hypoglycemic coma is contraindicated.

Farber (*J. Exper. Med.* **66**:405, 1937) suggested that the vasomotor control of the pulmonary vessels may be disturbed either by central or by peripheral disease and that occasionally acute pulmonary edema is dependent on such a disturbance. He termed this neuropathic pulmonary edema. The cerebral anoxemia induced by insulin shock therapy may produce a similar condition.

Moon and Morgan (*Arch. Path.* **21**:565 [May] 1936) showed that pulmonary edema frequently followed experimentally induced shock. An uncompensated disparity between the volume of blood and the volume capacity of the vascular system resulted in increased vascular permeability, accompanied by hemoconcentration and circulatory insufficiency. The shock syndrome therefore may also be related to acute pulmonary edema following insulin therapy.

In explaining the pathogenesis of the pulmonary gangrene in this patient, the presence of subclinical bronchiectasis must be considered as a locus minoris resistentiae. Aspiration of infected material from the mouth, with plugging of a small peripheral bronchus, probably occurred. Fulminating infection of an anaerobic type peripheral to the block probably resulted in involvement of the interstitial tissue, with abscess formation, surrounding edema, vascular engorgement and gangrene.

DISCUSSION

Dr. Herbert Freed: From my experience with insulin shock therapy, I am inclined to believe that pulmonary edema is more common than one finds it reported in the literature. Saxe and I reported on such cases (Prolonged Non-Hypoglycemic Coma Occurring During the Course of Insulin Shock Therapy, *J. Nerv. & Ment. Dis.* **90**:216 [Aug.] 1939). At least 1 or 2, and I believe 3, patients had pulmonary edema during the course of prolonged nonhypoglycemic coma. It is my belief that the cause of this pulmonary edema is neuropathic. I can recall another patient in whom pulmonary edema occurred on more than one occasion. I believe that it is more likely to develop in some patients than in others. Epinephrine might make the patient more susceptible to pulmonary edema, but, from my experience with its use, I cannot agree with Dr. Furst that it is the cause.

Dr. Thomas K. Rathmell, Norristown, Pa.: The suggestion of hyperepinephrinism as the cause of pulmonary edema is applicable to this case, as this is one of the well known pharmacologic effects of the drug. Reference to the pharmacologic effects of epinephrine (Pharmacologic Action of Adrenalin, in Piersol, G. M.; Bortz, E. L., and others: The Cyclopedia of Medicine, revised edition, Philadelphia, F. A. Davis Company, 1939, vol. 1, p. 166) shows that acute pulmonary edema constitutes the precursor of death in acute epinephrine poisoning.

Insulin, of itself, causes an outpouring of the hormone (preceding reference, pages 170-171). Hyperepinephrinism, therefore, is a possible entity which must be considered in cases of patients subjected to insulin therapy, particularly when they are given epinephrine hypodermically and pulmonary edema subsequently develops.

Toxic Psychosis Due to Thiocyanates: Report of a Case. Dr. M. R. Plesset, Norristown, Pa. (by invitation).

The literature on toxic psychosis due to thiocyanates is briefly reviewed, and a case is reported. The patient had hypertension and had been given elixir of sodium thiocyanate in another hospital. The resulting psychosis resembled that associated with bromide intoxication. The first determination of blood cyanate gave 20 mg. per hundred cubic centimeters. The chloride content of the blood was 1,025 mg. per hundred cubic centimeters. Both values decreased rapidly as the patient improved.

DISCUSSION

Dr Manuel Pearson: I had experience with 2 cases of the psychosis precipitated by treatment with thiocyanates. One patient, a woman who had been transferred from the medical ward of the Philadelphia General Hospital, was in the service of Dr. Winifred Stewart. She had been given sodium thiocyanate, and the level of the drug had evidently been closely watched. A typical psychosis developed. The woman died later; in the literature I found only 6 similar cases in which the outcome was fatal. The second patient, in the service of Dr. Baldwin L. Keyes, had been transferred from the neurologic ward with the diagnosis of subarachnoid hemorrhage. A true toxic psychosis was suspected. Later the family physician reported that he had been treating the patient with thiocyanate. At the hospital we estimated the level only after the patient had recovered from the psychosis; it was then 17 mg. per hundred cubic centimeters. The level evidently had been much higher while the patient was psychotic.

Effect of Vitamin B_1, Sucrose and Sorbitol on Certain Complications of Insulin Hypoglycemia: A Clinical Report. Dr. Thurston D. Rivers (by invitation).

Recognition of the role of vitamin B_1 in intermediate carbohydrate metabolism naturally led to its use in termination of refractory hypoglycemic states. Labbe, Nepveux, Gringiore and Freudenberg have shown the favorable effect of vitamin B_1 on certain toxic hypoglycemic symptoms. Demole has shown the antihypoglycemic and anticonvulsant effect of vitamin B_1 in normal rabbits given injections of insulin. In his opinion, it not only diminishes the frequency and intensity of the convulsions but also shortens the duration of the hypoglycemia. This, he concluded, was because of its beneficial effect on the removal of toxic intermediate carbohydrate products. The favorable modification of the intracellular oxybiotic process by vitamin B_1 was the rationale which prompted its use.

I believe that the intravenous administration of vitamin B_1, in 20 to 50 mg. doses, early in the stupor alleviates somewhat the central respiratory depression and the marked evidence of hyperkinesia, which, like the signs of hyperexcitation of the cardioregulatory center, may be precursors of convulsions; all this allows for a less stormy period of stupor. The degree of benefit from this type of therapy is variable. Certain patients show more marked benefit than others; the most striking results I have seen were the arrest of precipitant convulsions and, at times, the temporary partial restoration of consciousness.

The use of hypertonic solutions of polysaccharides to facilitate cellular dehydration has received attention for some time. The effects of a hypertonic solution of dextrose are sufficiently well known to establish its value clinically. The use of sucrose as a more effective agent in accomplishing cerebrocellular dehydration

without a secondary rise in cerebrospinal fluid pressure is dependent on its excretion unchanged by the kidneys and the relative impermeability of the blood–cerebrospinal fluid barrier. Masserman (*Bull. Johns Hopkins Hosp.* **57**:12, 1935) and the Mayo group have reported on this action. The search for more efficacious dehydrants has led to the use of sodium arabinate by Drabkin and Ravdin (*Am. J. Physiol.* **118**:174 [Jan.] 1937) and of dextrosorbitol, mannitol and styracitol by Car and Forman (*J. Biol. Chem.* **128**:425 [May] 1939) and Todd, Myers and West (*J. Biol. Chem.* **127**:275 [Jan.] 1939).

Sorbitol, a hexahydric alcohol with enormous water-binding capacity, has 1.88 times the osmotic pressure of sucrose; a relatively slight amount passes the cerebrospinal fluid barrier, but it has the noteworthy disadvantage that 39 per cent is converted into dextrose, which for the present purpose raises the dextrose concentration of the blood to a stupor-interrupting level.

For some time I have been using a 50 per cent solution of sucrose as an adjuvant. The striking effects are noticeable in several spheres. Neurologically, pathologic reflexes developing during stupor may be abolished; there are disappearance of myoclonic twitchings and clonic jerks, diminution of tonus and relief of laryngospasm and decerebrate rigidity; moreover, except in the occasional case, if administered at the proper time, it acts as a convulsive prophylactic. The depth and duration of the stupor do not seem to be affected. Metabolically, there is no elevation in the dextrose concentration of the blood. Unfortunately, nephrotoxic effect has been reported to follow its prolonged use. This is demonstrated in the diminished concentrating capacity of the kidney, as well as in decreased clearance function. Psychiatrically, the most interesting features are the increased clarity of contact (within the limits of the existing psychosis) following the interruption of the hypoglycemic state, and freedom from post-treatment headache and sluggishness. Its usefulness is still further enhanced by its value in the prophylaxis and treatment of prolonged coma. I plan to report more fully on this elsewhere and am convinced of its efficacy.

Sorbitol has many of the same effects; in addition, however, because of its glucogenic properties, the termination of stupor usually follows within thirty minutes its administration. This makes it valuable in the treatment of prolonged comas.

DISCUSSION

Dr. M. R. Plesset, Norristown, Pa.: About a year ago, when working with insulin, I made occasional use of vitamin B_1 to terminate prolonged coma. I was not successful in any case. In my cases the termination either was spontaneous or would have occurred without vitamin B_1.

Dr. Herbert Freed: My colleagues and I use vitamin B_1 also in management of prolonged nonhypoglycemic coma. We were using it before Dr. Freudenberg reported that he had found it invaluable (Use of Vitamin B and B_2 in Insulin Shock Therapy of Schizophrenia, *Wien. klin. Wchnschr.* **50**:535 [April 23] 1937). The vitamin was used prophylactically; 1 patient, nevertheless, went into coma. Perhaps we were not giving a sufficient dose. At that time a total of 50 mg. was considered to be a tremendous dose. We used 10 or 20 mg.

Dr. Thurston D. Rivers: I am sorry I did not make myself clear. We are using vitamin B_1 not to terminate stupor or hypoglycemia but merely as an adjunct to treatment. In cases in which early neurologic signs and hyperexcitation are present we have found vitamin B_1 in doses of from 20 to 50 mg. to be of benefit. I mentioned the use of sucrose and sorbitol in the long stupors, but none of my comments were intended to carry significance other than that the substances were used during regular stupor and as routine treatment.

I wish to remark on gangrene of the lung, which has been discussed. I notice that there was evidence of pulmonary edema after the intravenous injection of a 50 per cent solution of dextrose. I may add, as another possible cause of edema, that dextrose in high concentration injected into a vein at a rapid rate would

certainly in itself produce pulmonary edema by overloading the venous stream and the tissues. That might be, I do not say it is, one of the factors which entered into the pulmonary edema in the case reported.

Intellectual Frustration: Behavior Difficulties in Superior Children. Dr. Melvin W. Thorner and Dr. Gerald Pearson.

Behavior disorders in general are considered evidence of essential disharmony between the person and his environment. In the 7 cases presented, the intellectual needs of these superior children found no satisfaction in the home and school environment. This resulted in behavior disorders, many of the components of which were expressed in emotional symbols. The characteristics of the disorders were lack of evidence of anxiety and absence of schizoid traits and of marked autistic thinking. Fantasy formation was slight, and discussions were largely factual. Perhaps the most outstanding trait was very aggressive behavior. The treatment in these cases consisted of a study of the individual child and his intellectual needs, and of the sufficiency of the environment for the satisfaction of these needs. In all the cases provision of adequate intellectual outlets formed the basis of the active portion of the therapy. The relation of the "speed-up" and the "enrichment" school programs was discussed. It was stressed that the mechanism of intellectual frustration was most apparent in superior children, but that it might be a factor in normal children and in adults.

DISCUSSION

Dr. Gerald Pearson: I think the field of child psychiatry has progressed to the point where it should be possible to delineate among children's problems certain clinical entities with a common etiologic and psychopathologic basis. Such a procedure would enable therapy to proceed more rapidly and certainly. Therefore, when Dr. Thorner consulted me about this series of cases, I discussed with him the possibility of discovering a symptom complex that would enable one to know early that the child's difficulty lay in the starvation of his intellectual capacities. I do not think that we have succeeded in defining such a symptom complex. The symptoms presented by these children are not different enough to be distinguished from those presented by children suffering from a different psychopathologic condition.

Dr. O. Spurgeon English: As I listened to this paper I questioned the advisability of making any subdivision of these cases on the basis purely of intellectual frustration. If any such attempt were made for the purpose of clarifying the approach to treatment I should still be reluctant to think of them as presenting other than a problem of emotional frustration and should suggest the designation of "emotional frustration due to intellectual starvation." If I am hungry and dinner is late in being served I may be emotionally frustrated, and if there is something interesting going on and no one will tell me about it I may also be emotionally frustrated.

I think it dangerous to make any special grouping of cases on the basis of intellectual frustration alone, since it seems doubtful whether any child with a neurotic problem has not had some frustration in his urge for fact finding.

Dr. Lauren H. Smith: Does Dr. Dozier see any such frustration factor in cases of reading disability or similar situations?

Dr. Paul Dozier: I agree with Dr. English. I should classify the cases as those of emotional frustrations. This, of course, is a minor point.

In comparing the children under consideration with children who have disabilities there are two distinctions: The superior children did not have much anxiety, and children who are bright but have some reason for failure to perform up to the level of their intelligence usually have anxiety, which anxiety may or not be masked. Also, in the cases which Dr. Thorner mentioned the treatment

was comparatively short and simple, and in the end evidently provided a good adjustment, or the patients would be returning. (I do not know how long this series has been studied.) The more important difference has probably to do with the absence of great anxiety. The type of child discussed by Dr. Thorner feels consciously that in most respects he can compare himself with an older and a superior group, whereas the child with a disability, if he feels he cannot compare favorably with his own group, is faced with comparison with the younger group, which is not a welcome necessity. The situations are quite different in this respect.

DR. W. COLE DAVIS, Atlantic City, N. J.: I wish merely to state that these children appear to offer the most satisfactory problem in mental hygiene because of the good results from treatment usually obtained. I recently saw such a child in the mental hygiene clinic at Atlantic City. His intelligence quotient was far superior to that of any other child in his grade, so he was transferred to the next higher grade, where he has had no difficulty in keeping up with the work and is no longer a behavior problem.

DR. MELVIN W. THORNER: Probably I cannot answer the questions raised in this discussion. Both Dr. Pearson and I have still a great many unanswered questions of our own. We are not enthusiastic about splitting off artificial portions of mental activity. Mental activity is presumably a highly integrated and intradependent organization, and what happens in one part of this organization must have its reverberations in others. However, for purposes of study, it may be permissible to separate the Cheshire cat from its grin, if a full awareness of the hazards accompanies the procedure.

One of the reasons leading to the choice of the term "intellectual frustration" was the wish to imply a parallelism with "emotional frustration," with discussions of which psychiatric literature is replete. The situation implied by this term is well known to educators, and in some instances adequate methods (which we indicated) have been devised to cope with the difficulty. In many localities no efforts are so expended. The importance of an adequate, preventive and possibly therapeutic setup is obvious if these future scientists, engineers and thinkers are to be given an efficient start.

Many of the symptoms of these children might be termed "emotional," but we believe that the primary and causative factor is the frustration of intellectual drives. This shaving of edges in order to present a clearly delineated picture need not be defended, for that is the basis of all biologic data.

Psychiatric Aspects of Carbon Disulfide Poisoning. DR. FRANCIS J. BRACELAND.

This report concerns the psychiatric aspect of a study of carbon disulfide poisoning the neuropathologic portion of which is the subject of a paper by Alpers and Lewy (Changes in the Nervous System Following Carbon Disulfide Poisoning in Animals and in Man, this issue, p. 725).

Acute carbon disulfide intoxication is comparable to the narcotic effects of other anesthetics. Chronic absorption of carbon disulfide is associated with the physical change described by Lewy and attributed to hepatic damage and subsequent vitamin B deficiency.

My survey convinces me that there can be no doubt of the existence of a toxic psychosis due to carbon disulfide. In the carbon disulfide psychoses the following characteristics are noted: confusion, assaultiveness, hallucinations, delusions, depression and, finally, amnesia for the acute attack. While the onset of the psychosis is usually acute, a gradual change in personality would have been noted by attentive observers. This change is insidious and is accompanied by a phase of irritability, depression, headache and insomnia. The libido is lessened, and dreams of a terrifying nature occur. The break frequently comes while the patient is at work.

It is probable that carbon disulfide also acts as an *agent provocateur* in persons who are already predisposed to mental illness. A larger group of workers display symptoms of a chronic form of absorption and intoxication. Apparently, these symptoms are dependent not on physical habitus or heavy exposure to the gas but on individual susceptibility to carbon disulfide.

The toxic syndrome consists of the following symptoms, which are fairly constant: (1) personality changes (always for the worse); (2) marked irritability; (3) memory defect; (4) insomnia; (5) bad dreams; (6) lessening of libido, and (7) constant fatigue. It is apparent that once a person has shown evidence of toxic symptoms he should be removed from further exposure to the chemical and never again be subjected to it in large quantities or in heavy concentrations. It is essential that a vitamin-rich diet be procurable in the restaurants and homes of workers in carbon disulfide.

DISCUSSION

DR. BALDWIN L. KEYES: A few years ago I had an opportunity to examine 2 employees of a viscose rayon plant who showed toxic symptoms, supposedly due to carbon disulfide intoxication. The symptoms were chiefly manifested as paranoid ideas and aggressiveness toward the foreman. In the first case, that of a young girl who had recently been employed, diagnosis was toxic psychosis, possibly due to carbon disulfide poisoning. It was suggested to the company officials that the air in the room in which she worked be examined for carbon disulfide content. The amount found was said to have been too minimal to be a responsible factor, and it was pointed out that no employee in that room had had a similar illness. However, while this patient was convalescing similar symptoms developed in the girl who took her place; this time the question was raised whether they may not have resulted from hysterical simulation. Further study of the situation showed that both these girls had been placed in the closed-in corner of a large room, without the ventilation which was available to other workers near them. A window was knocked out in that vicinity to establish proper ventilation, and no other cases occurred. It would seem that the possibility of individual hypersensitivity, which Dr. Braceland mentioned, is an important matter to consider.

DR. JOSEPH C. YASKIN: What happens in cases of these toxic manifestations after the patient has been removed from his work for a time? After signs of irritability, insomnia, loss of libido, fatigue and some of the marked neurologic abnormalities develop, can the person recover after being removed from the industry for a period, and to what extent?

DR. CHARLES RUPP JR.: I wish to ask Dr. Braceland what is the approximate incidence of carbon disulfide psychosis. Does he have any information as to whether persons affected by carbon disulfide were more indulgent in the use of alcohol than normal?

DR. MELVIN W. THORNER: There is one aspect of Dr. Braceland's work which has invited the attention of persons other than physicians. This was brought to my attention when I was asked to examine a former worker in a viscose plant. His symptoms had somewhat mimicked those that Dr. Braceland has described. A full consideration of this man's situation led to the conclusion that his disabilities were psychoneurotic rather than toxic. Dr. Lewy saw him and arrived independently at the same conclusion. Probably one can anticipate a rise in the number of such cases in the future, and an intimate knowledge of the symptomatology of this toxic syndrome will be necessary for a differential diagnosis.

DR. JOSEPH C. YASKIN: With regard to Dr. Thorner's observation, it is true that neurosis simulating neuroses does occur. The reverse is more often the case. A great many industrial problems are overlooked. In many a case of lead or manganese poisoning the condition is still treated as a neurosis. All that is required is more diligent investigation in order to obtain absolute evidence of lead intoxication. I have not had much experience with carbon disulfide

poisoning, but the patients, to my mind, would have to be good Barrymores to lead one to believe that they were simulating. This particular poisoning has profound effects on behavior and the structure of the nervous system, and it is for this reason that I raise the question of what happens to these patients when their symptoms are relieved.

DR. ROBERT A. MATTHEWS: I wish to ask Dr. Braceland what concentration of carbon disulfide in the air is toxic, how long an exposure to a toxic concentration is generally required to produce symptoms and whether this substance permeates clothing and other sources of material. I have heard an amazing story of how the wife of a viscose worker was made ill by the inhalation of fumes from her husband's clothing.

DR. FREDERIC H. LEAVITT: In what types of industries are workers apt to be affected with this condition?

DR. O. SPURGEON ENGLISH: I wish to ask Dr. Braceland the following questions: 1. In how many of these cases did parkinsonism develop? 2. What did the brain show post mortem?

DR. FRANCIS J. BRACELAND: The reason for not wanting to discuss the sociologic aspects of this work is apparent. One government official was in trouble for so doing. These cases are now in litigation, and all of us who have been attached to the survey have known from the start that we could not become involved. Capable men are taking care of the legal side, and we are therefore not shirking our duty.

With respect to Dr. Keyes's observation concerning the girl who worked in a portion of a spinning room which was not ventilated: Such a situation is not at all infrequent. A door could be knocked out for the purpose of ventilation, but it seems that this interferes with the texture of the silk. The moisture must be kept at a certain level. The workmen did not agree with this, however, and said they used to make just as good silk when the windows were open.

In reply to Dr. Yaskin: It happened in this case that the men were on strike for about nine months. About 75 per cent of their clinical symptoms disappeared during this time. My associates and I were not able to examine all of the employees because, unfortunately, they were afraid of losing their jobs. We saw some of the men who had been fired; within ten days they were much improved clinically. Apparently the reaction is reversible to a certain point.

With regard to Dr. Rupp's question as to how many patients had overindulged in alcohol: We omitted every one who we thought was addicted to alcohol. We refused to consider cases in which we saw all the symptoms but in which alcoholism was suspected, because we had not determined just how much alcohol might affect the picture. We thought it probable that we would be asked this question. As soon as we could confirm the alcoholism we eliminated the cases from the survey.

A personal observation concerned with the same question was given us gratuitously. A general practitioner, who was in no way connected with the survey, told us that the people who lived near the mill and whose houses were permeated by odors from the mill carried on in an uninhibited fashion.

In answer to Dr. Thorner: As far as compensation is concerned, I am afraid there will be chicanery.

In reply to Dr. Matthews' query regarding the toxic concentration: Ten parts of carbon disulfide per million is a safe concentration. When we suggested this as a concentration to be employed, we were told that it could not be done. Other companies have been able to do so, however.

The men were forbidden to put their heads into the churns. It is not easy to clean a churn without doing so. Just how long before carbon disulfide produces effects we do not know—some persons were quickly affected and others not at all.

DR. ROBERT A. MATTHEWS: Then, can some people work in these plants for years?

DR. FRANCIS J. BRACELAND: Yes. There is no way of telling in how many persons psychoses developed, because we could not secure the people we wished to examine. We did examine 120 persons. Bear in mind that we were not regarded in too favorable a light and that we had to take whom we could get for examination.

In some workers who had been in the plant for twenty-five or thirty years we found no symptoms. We believe such symptoms are due to individual susceptibility to carbon disulfide. Dr. Lewy tells of a woman, not psychotic, who exhibited variable neurologic signs developing from fumes inhaled from her husband's work clothes hanging in the room.

As to Dr. Leavitt's question, carbon disulfide is considered irreplaceable in the preparation of cellulose xanthate, in the process of manufacturing what is known as india rubber and in the viscose rayon industry.

As to the number of cases in which parkinsonism developed, I must refer you to Dr. Lewy. This was his part of the survey. However, there were not many such cases. F. M. R. Walshe has described several cases of parkinsonism associated with carbon disulfide poisoning.

LAUREN H. SMITH, M.D., *President, in the Chair*

Regular Meeting, April 12, 1940

The Rorschach Experiment. DR. EMIL OBERHOLZER (by invitation).

The paper sets forth certain points regarding the fundamentals and principles of Rorschach's experiment and contains statements regarding its development and validity in the diagnosis of personality and psychiatric conditions. The experiment's premise holds that the process of perception and apperception embodies the intelligence and endowments of the whole personality, its emotional capacity for experiencing and living, together with its variegated disturbances. The basis of the experiment is the countless perceptive possibilities that it offers. The interpretative answers presented to the test form the basis for the experimental factors, and summation of these answers represents the experimental findings in each case.

The criteria for an objective determination of whether an answer is a good or a poor form, a normal or a small detail, a form-color or a color-form response are discussed. Rorschach, by combining the statistics with the results of constant and careful comparison of experimental findings and clinical factors for a variety of persons, such as the intelligent and the unintelligent, the emotionally stable and the emotionally unstable, established the psychologic meaning of the various factors that make up the test. He found, for instance, that a person's affectability and character are related to the total of the various color answers, as well as to the ratio of movement and color answers.

An attempt is made to show how the experiment covers the manifestations of the emotional variety in normal and in pathologic life. The paper then discusses the importance of correlations between the experimental factors. These correlations are the core of the experiment and are indispensable in the evaluation of the findings with the test. A number of factors, perhaps all of them, are as much indications of the intelligence as they are part and parcel of the affectivity, and are important representatives of certain normal and pathologic emotional conditions. What they are depends on the sum total of the findings, and the factors must never be considered or interpreted separately.

Finally, the paper reviews the widespread applicability of the test, provided that certain prerequisites, such as adequate training, experience and a broad outlook on the material of experimental findings, are fulfilled.

DISCUSSION

DR. CARL BINGER, New York: A certain English philosopher, whose name I believe is anathema in Brooklyn and the Bronx, described the sun as simply "waves of probability." When I first encountered the Rorschach experiment, I might have described it as "waves of improbability," but I have learned that it resembles the sun in actually throwing light where there was darkness. I am not qualified to discuss the theoretic aspects of the experiment. I am familiar with the test in its more practical clinical application to diagnosis, prognosis and indications for treatment. A procedure which has objective validity, such as this has, must be welcome to psychiatrists, for there are too many loopholes in one's knowledge. Statistical material is poorly organized. Concepts are ill defined. Too often one must grope in the dark, working intuitively and drawing inferences from insufficient data. It is gratifying, therefore, to have one's judgment checked and sometimes corroborated by a more objective method.

I shall now give a few examples of the help that the Rorschach experiment, as performed by Dr. Oberholzer, has been to me in the handling of patients. Two young male college students have both had difficulty in remaining in college because of certain rather similar symptoms. One student had to leave the classroom frequently because of a need to go to the toilet. He had a predilection for sitting in the back of the classroom, near the door, and felt uneasy whenever he sat far from the exit. The other student had much the same difficulty. He did not like high-ceilinged lecture rooms. He always sat near the door when he could. Both young men were depressed and withdrawn and had thoughts of suicide.

In the first case, the diagnosis, based on the Rorschach report, was "neurosis in a schizoid person with latent dementia praecox." In the other case, in which superficially the situation resembled that in the first, Dr. Oberholzer reported that the patient was in a state of depression; psychogenic depression and schizophrenia were ruled out by the test; the diagnosis was therefore neurotic depression. This important differential diagnosis not only corresponded to my own impression of the 2 patients but influenced me in my judgment concerning therapy.

A woman aged 38 consulted me because of what she called "feelings of unreality." She noticed such feelings often when she entered a room. In addition to this symptom, the patient complained of poor sleep, inability to relax, anxiety states mounting almost to panic and many symptoms suggestive of hysterical conversions. Because of the "feelings of unreality" and certain other characteristics of this patient, I suspected petit mal. I learned that her mother had been epileptic since the patient's childhood. Her only sister was schizophrenic and had committed suicide. Dr. Oberholzer picked out from results of this patient's Rorschach test both the epileptic and the schizophrenic trends, but concluded that the diagnosis was "anxiety neurosis developing toward conversion hysteria."

I wish to bring out one more point. It has to do with prognosis and the related problem of indications for psychoanalytic therapy. There can be no doubt that better criteria are needed for the use of this treatment. The argument "We can't do anything else; we might as well use psychoanalysis" is scientifically unsound. One must look for specific indications and have at least some general sense as to what the prognostic situation is. In my experience the Rorschach experiment can be of decided help, not only in selecting patients who will benefit from psychoanalytic treatment but in giving foreknowledge of the anticipated results.

DR. LAUREN H. SMITH: When a person is experienced with the Rorschach experiment, he may administer the test without necessarily knowing the history, the nationality, the story of the illness or anything about the patient. The material is given as a cold, objective test. From the results the administrator writes up his impression of the subject's personality from the clinical point of view, or on the basis of pathologic evidence indicated by the study. It is certainly

valuable to have something as objective as this test to check or to confirm the clinical diagnosis. It is much like a laboratory test in its uses as an aid. I have known instances in which material has been sent to Dr. Oberholzer and from that material alone he has formulated an impression of the patient, has pointed out facts about the personality, occupation and attitudes, and has made a diagnosis which verified that of the clinician who had actually seen the patient.

Dr. John C. Urbaitis: I have been practicing technic of the test and comparing the results with clinical observations. In persons who have poverty of emotional life, there are no color responses which can be scored. In those who are engrossed in psychoses, however, the prints seem to elicit a soliloquy with no apparent reference to their content. The patients who are in excellent contact with their environment give a large number and variety of responses. It is easy to recognize the patient with superior intelligence and the one who is a good subject for intensive psychotherapy.

Dr. Herbert Freed: I have been interested in this experiment since I have been at the Philadelphia General Hospital, but I find that I am still learning as I work with it. I have found Dr. Oberholzer's presentation interesting.

Dr. Howard Rome: With regard to the classification, can the results of the Rorschach experiment differentiate manic-depressive psychosis from involutional melancholia?

Dr. Lauren H. Smith: Is it possible with the Rorschach experiment to make a differentiation between a manic-depressive and a psychoneurotic depression?

Dr. John C. Urbaitis: There are answers which cannot be scored readily, as when a patient looks at one of the black forms and states that it looks like blood, or a patient displays perseveration in saying that the forms are just ugly blots. In 1 case there were four or five responses of "blood" when there was no red color to stimulate this reaction. The patient was a person who had had an apoplectic stroke about four months previously, and memory for recent events was poor. In addition, it was difficult to hold the patient's attention.

Dr. Emil Oberholzer: The black spots are frequently interpreted as blood by persons with organic disorders—not patients with dementia paralytica but those suffering from residuals only, such as follow apoplexy or multiple sclerosis. These reactions are color answers and may concern a whole or a detail.

Answers which are not, or seemingly not, scorable, occur in many conditions, even in "normal" persons—the very meticulous and precise persons who describe the pictures instead of interpreting them. If one notices what they pick out one can do the scoring for the whole-part issue. They are form, chiaroscuro or color answers when they describe the forms and outlines or the shadings and colors of the pictures. The persevering response of "ugly blots" is a description of this kind which includes an emotional expression. These descriptive reactions often occur in neurotic persons and in patients with organic mental disorders, such as traumatic constitution and encephalitis lethargica.

As to perseveration: When the same answer is given throughout the experiment, as often happens in children, the test is of no value. The best one can do is to repeat the test, urging responses other than the perseveration. In this way one will be successful in almost any case.

With regard to the differentiation of manic-depressive and involutional psychosis, it is theoretically possible, as it is possible and comparatively easy to make a differentiation between a manic-depressive and a psychoneurotic depression. I say theoretically, because I have had no experience with the Rorschach test in cases of involutional psychosis. The differentiation between a manic-depressive and a psychoneurotic depression is based on the color shock. If there is no color shock at all, neurosis is ruled out. In a case of psychogenic, but not of neurotic, depression, when a patient is suffering from a heavy loss for instance, there is no color shock but one finds, on the one hand, manifestations of melancholia and, on the other, some movement answers, as well as other signs which are missing in melancholia characteristic of the manic-depressive psychosis.

DR. LAUREN H. SMITH: Will Dr. Oberholzer explain color shock?

DR. EMIL OBERHOLZER: I did not mention color shock, since to do so would have made the presentation too detailed. Color shock is the point at which the patient falters and "staggers" at one of the colored pictures. The ordinary color shock occurs in relation to one of the many colored pictures, usually to picture VIII. The person hesitates; his associations are blocked for a while, sometimes for a very little while, but just long enough to make a difference between his response and his previous reaction to the black forms. The same manifestations can repeat themselves with pictures IX and X, or they may have already occurred in response to the red of pictures II and III. They are always characteristic of neurotic conditions.

I have been asked: "Can you differentiate the mentally ill from the feebleminded in contrasting deteriorating patients with mental disease and feebleminded patients of approximately the same mental level?" Numerous differences are evident. Not only are the experimental findings in cases of the feebleminded conspicuous and almost specific, so that it is not easy to confuse them with those for the mentally ill (schizophrenic persons, for example), but in cases of deterioration one finds among its signs some manifestations of the original intellectual level. Even in a case of advanced dementia paralytica one still obtains some good or even very good answers, which are never produced by the feebleminded. There is no doubt that the deterioration is something that has been acquired through the illness. The same is true of the traumatic constitution, as I have previously pointed out (Zur Differentialdiagnose psychischer Folgezustände nach Schädeltraumen mittels des Rorschachschen Formdeutversuchs, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **136**:596, 1931).

As to the anticipation of the outcome of insulin or metrazol shock therapy by the Rorschach experiment, I do not know. I have no experience, but it does not seem unlikely, since it is possible from the experimental findings to reach conclusions as to the prognosis with psychotherapy. However, I am doubtful as to how much it means in the final results.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

R. GORDON BRAIN, M.D., *President, in the Chair*

Regular Meeting, March 14, 1940

Spontaneous Subarachnoid Hemorrhage. DR. DAYTON SALON, Ann Arbor, Mich.

The thesis of this paper is that spontaneous subarachnoid hemorrhage is more common than is generally realized and that if it is promptly recognized and properly treated the prognosis is relatively good. In the five years from January 1935 to January 1940, 62 patients were treated for a total of 68 attacks of spontaneous subarachnoid hemorrhage in the University Hospital at Ann Arbor, Mich. In this series there were only 9 deaths, a mortality rate of 14.5 per cent. This relatively low mortality is due in part to the fact that patients often do not reach this hospital unless they survive the initial, and most critical, stage of the illness. Autopsy was performed in 7 of the 9 fatal cases. In 3 of them there was malformation of vessels of the circle of Willis, with rupture of aneurysms, and in 2 cases marked atherosclerosis of the basilar cerebral vessels, without the exact source of the hemorrhage being found; in 2 cases no pathologic change was observed to account for the hemorrhage.

In most of the cases the well known classic syndrome of the disease was presented. Atypical cases were those in which signs of meningeal irritation were delayed or did not appear at any time and those in which a syndrome of a cerebral

lesion alone was present. Cases in which there developed marked increase of intracranial pressure with associated papilledema offered especial difficulties in diagnosis and treatment. The Ayala index was of no value in ruling out massive expanding intracranial lesions. The treatment resolves itself into measures to combat shock and increased intracranial pressure and to afford the patient as much symptomatic relief as possible in order to avoid emotional and physical factors that might cause additional hemorrhage. Lumbar puncture and manometrically controlled drainage of the cerebrospinal fluid, to avoid sudden changes in dynamics, give the patient much symptomatic relief, and it is believed that judicious spinal fluid drainage on symptomatic indication may be safely employed in the treatment of subarachnoid hemorrhage. No complications followed lumbar puncture in any of the cases in this series.

Murderers and Sexual Psychopathic Offenders: Psychiatric Aspects of New Procedures in the State of Michigan. DR. RALPH M. PATTERSON, Ann Arbor, Mich.

Prior to the termination of the eighteenth century, the psychiatrist played little or no role in the criminal court. Since, there has been an increasing demand for expert testimony, in keeping with the broadening concept of irresponsibility. During the past fifty years attempts have been made to extend this concept to include borderline mental conditions and "irresistible impulses." As a consequence of this and the manner of questioning, psychiatric testimony acquired an unsavory reputation. The state of Michigan has made definite advance in the field of criminology by providing for psychiatric examination of defendants charged with murder and of persons alleged to be sexual psychopathic criminals. Although these laws possess certain handicaps, they offer the psychiatrist an opportunity to present to the court a written case study, i. e., a report of the complete longitudinal section of the accused's past, present and future. By presentation of adequate, practical and conservative case summaries, the psychiatrist's reputation may be elevated and the courts convinced of the advantages of individualized criminologic methods. By forsaking the punitive approach, the recommendations of the American Bar Association may be fulfilled. With further progress one might look forward to the establishment of a "treatment commission," composed of a social investigator, a psychologist, a psychiatrist and others as indicated. All offenders would then be committed to this commission, and corrective measures, preventive detention, hospitalization, parole and probation would be under its supervision. Confusing and contradictory expert testimony, now so prevalent, would be largely eliminated from the courts. The general trend would be to avoid placing more criminals in psychiatric hospitals and to place more psychiatrists in the field of criminology.

DISCUSSION

DR. LOWELL S. SELLING, Detroit: The paper which Dr. Patterson has presented touches on a subject which is close to every one in this state. Probably no effort in jurisprudence has been carried on in a more obtuse, inept manner, and with as good purpose, as that dealing with the control of the sexual psychopathic offender. One must not forget that there was specific need for such legislation in the mind of the public and that this need was met in the legislature by capitalizing on the effect of the heinous act committed by Merton Goodrich. Without this vicious offense, the people of Michigan would have been in the same apathetic state as those in other commonwealths.

Dr. Patterson is in error when he says that interest in the subject dates back to 1937. The original Goodrich Law was passed in 1935, but the acts of 1937 and 1939 have not been known by the same name. The act of 1939 has been known in the Detroit court as the Selling Act, because I was associated with its passage; when I asked the judges their opinion on its constitutionality they said that it probably was unconstitutional, and gave it my name. Nevertheless, the law which they saw was not the one which Dr. LaBine, Dr. Moloney and

I advocated at a meeting of a committee which included Judge Van Zile and Governor Murphy. It was a revision of the law passed in 1935. As I see it, the gist of the whole matter is this: There is no need to single out the sexual psychopathic person from all others with psychopathic tendencies. Why should the one group of persons showing psychopathic behavior be given hospital treatment and not others of the same type? And why, as has been brought out frequently by Dr. Robertson, should an incurable psychopathic criminal, who needs only incarceration, occupy a bed in a hospital which could be used for a better purpose? The answer, of course, lies not in law making, as Dr. Patterson seems to have emphasized, but in changing the point of view of both the courts and the prison administrators. This purpose has been accomplished to some extent, so far as the attitude of the judges is concerned, in the Detroit court. The patients are now sentenced to prison, in many instances, with a specific therapeutic aim; in that case, if therapy can be carried out at the Jackson State Penitentiary rather than at Ionia State Hospital, I see no need for hospitalization. The point to be emphasized is that the sentence should not be determinate and that its purpose should be therapy rather than segregation. In considering the latter, however, one must not forget that psychiatry has not yet reached the point at which one can treat all criminals; the condition of a certain number can be diagnosed in the clinic as incurable, and these persons should therefore be segregated.

The present law is an unfortunate one. Dr. Patterson has given illustrations of how well it has worked; I could give innumerable examples of that side of the problem, as well as the other. I wish to point out first: The sex law of 1937 defeats its own purpose. There are persons who seem capable of benefiting from treatment. If the sexual psychopathy has lasted over a year and the person has a tendency to commit sex crimes—as the law defines it—he is much more likely to be therapeutically inadequate than a person who is apprehended early in his pathologic activity, especially one who has no previous record of arrest. The traumatism from arrests and convictions in the past must not be overlooked. The criticism may be raised here, which I answered in a previous paper read before this society (Results of Therapy in Cases of Sexual Deviation, ARCH. NEUROL. & PSYCHIAT. **43**:1276 [June] 1940), that there are available few adequate means of treatment of such criminals. I can refute this by pointing out that my colleagues and I have followed up, without noting further violation, many of the persons now in the clinic whom Dr. Robertson has turned loose; there are, however, a certain number from Ionia State Hospital who have not recovered within a certain period. If no attempt is made to devise means of treatment and to work on the problem diagnostic and forensic work will be futile.

Other problems in carrying out this sex law arise. First, if a person denies his guilt and has not yet been found guilty by the court, can it be established under the new law that he is sexually psychopathic? Do a previous conviction of and a present denial of guilt by an unstable psychopathic person indicate that he is likely to commit further sex crimes? I question this. Another problem arose in a case only this morning. Should one distinguish between a sexual psychopathic offender, and place him in a hospital for life, and an ordinary psychopathic person who has dangerous criminal tendencies. The case I have in mind is that of a man with a long criminal record; he has served time in all the Michigan penal institutions; among his other arrests was one for contributing to the delinquency of a minor, at which time he was living in a common law relationship with a girl he thought was 18 but who was only 16. Last November he was acquitted on a charge of rape. The clinic found that he was homicidal, dangerous, irritable and assaultive and had vicious sexual tendencies, but the only evidence of this is his behavior in 1936. As he denied any abnormal sexual occupations, his pathologic tendencies, as evidenced by his own statement and his record, are likely to be only in the field of depredation.

Another problem arises in the definition of the various terms. What is a sex criminal? Simply, of course, it is one who commits an act prohibited by

law; if, however, as in many cases of statutory rape, the act is condoned by practice and custom is he, from a psychiatric standpoint, a criminal?

Another consideration is that of borderline intelligence. A man may be feebleminded and yet be able to cooperate with counsel under the insanity statute; technically, nevertheless, he is feebleminded and should not fall into the group defined by the 1939 law; hence, he would go scot free. He should by rights be locked up in an institution for defective delinquents, such as the one in Napanoch, N. Y.

Dr. Patterson has pointed out the advantage of bringing out the past history and other information which a psychiatrist would use in reports to the court. From this standpoint I think he is naive. After much consideration of the problem of the court, I should say that under the present legal code in Michigan one is probably dealing more justly with criminals from the point of view of a functioning democracy when one does not permit a man to be locked up because he is "potentially dangerous." A prediction of future conduct is out of place because it is not legally admissible, and rightly so; I question the accuracy of most psychiatric predictions concerning persons who have not committed many crimes.

The recommendations of the American Bar Association have been taken into account by psychiatrists for a long time. There is no point in them which is not being carried and has not been carried in the Recorder's Court since 1920, but I find that a psychiatric report is better not filed as part of the record. It can be used against the man by the police when an attempt is made to rehabilitate him; it can be given to the man and do immense harm; so by common consent the Recorder's Court does not file these reports with the record, but keeps them in a separate locked file. Unfortunately, the American Bar Association does not know what a court clinic can do. It has no idea of prediction tables, tabulated types of histories or the use of the Rorschach test and the polygraph; all these carry the psychiatric report beyond simple psychiatry. In order to make valid the recommendations of such reports, there is needed associated with the court an extensive treatment clinic, as well as a completely indeterminate sentence and the ability of the clinic, as well as of the judge, to send convicts to designated institutions rather than to those which are mandatory, as has been the custom in the past. This brings up again the point in the 1939 law—that concerned with offenders committed through the State Hospital Commission. Unfortunately, the commission, as Dr. Patterson pointed out, has only one psychiatrist, and of course, its technic has become sclerotic. In 1 case I recommended the Ypsilanti State Hospital and in another the Eloise Hospital because I knew there were technics available in these hospitals which would be useful. Unfortunately, both the convicts were sent to the Ionia State Hospital.

The problem of psychiatry in the courts and in other organizations for dispensation of justice is extremely intricate. Dr. Patterson has reviewed competently for you the past history of psychiatric thought in this field. Unfortunately, in mentioning the Arnold case, he quoted the expression most frequently used—the "wild beast of the fields test" of responsibility. The issue is confused because the judge brought up the question of whether a person is good or bad inherently. Dr. Patterson has presented a good point of departure for future work on forensic psychiatry. Unfortunately, in the past too much consideration has been given by individual psychiatrists, including myself, to what a law in its interpretation would mean to one individually. It is only by frequent use of the law, frequent experience in court and frequent consideration of papers such as this that one can approach the subject with any degree of reasonableness.

Use of Colloidal Thorium Dioxide in the Diagnosis of Expanding Cystic Intracranial Lesions. Dr. E. A. Kahn (presented by Dr. Carl F. List), Ann Arbor, Mich.

During attempted ventriculographic examination or biopsy of a suspected tumor of the brain a cystic cavity may be entered. Visualization of such a cystic

lesion has the following advantages: It localizes the lesion directly and may give information as to its size. It may outline a mural nodule. The appearance of the cavity frequently suggests the pathologic nature of the underlying neoplasm; for instance, irregular, ragged cysts are seen in glioblastoma, while large, smooth-walled cysts with a mural nodule are seen in the cystic astrocytoma of the hemisphere. An encapsulated abscess of the brain has a smooth, round or oval outline, whereas a metastatic, nonencapsulated abscess has an irregular, slit-like appearance. Demonstration of a large cavity makes the surgical procedure easier and permits operation through a smaller incision.

The best contrast medium for the roentgenologic visualization of intracerebral cavitations is colloidal thorium dioxide. This substance is intensely opaque to roentgen rays and is water soluble. Since thorium dioxide mixes easily with any cystic fluid or pus, a small amount (5 cc.) is sufficient to outline even a large cavity. Thorium dioxide remains in place and is phagocytosed by histiocytes. This is of value in abscess of the brain, as it may demonstrate the capsule. Thorium dioxide injected into an abscess of the brain serves as an excellent indicator of a change in location of the abscess during subsequent operative procedures. It shows, for instance, how the abscess tends to migrate toward a bony defect or may even be spontaneously extruded.

When injected into a closed cystic or abscess cavity, colloidal thorium dioxide is innocuous; it is, however, highly irritative in the ventricular and subarachnoid spaces. Thorium dioxide, therefore, should not be used for visualization of the ventricular and subarachnoid systems. There is no danger of late damage resulting from the radioactive properties of thorium dioxide, as only a few cubic centimeters is used and the substance is subsequently removed at operation.

R. GORDON BRAIN, M.D., *President, in the Chair*

Regular Meeting, April 25, 1940

The Sexual Psychopathic Patient as a Psychiatric Problem. DR. DAVID LEACH, Detroit.

Limitations of the methods of classification prompted the study of 26 consecutive cases of sexual deviation among patients admitted to the hospital. With emphasis placed on the individual psychosexual development, significant relationships between the specific deviation and earlier influences were frequently found. Seduction, precocious stimulation and castration threats in childhood were prominent in some cases; in others, important factors remained unconscious and inaccessible. Fantasy formation appeared as the setting for various deviations. Sufficient evidence warranted the view that a psychogenetic approach to the sexual deviation offers a fruitful means of investigation.

DISCUSSION

DR. HENRY A. REYE, Detroit: I commend Dr. Leach on his excellent paper on this difficult subject. I am glad he did not limit himself to descriptions and classifications. He searched for a unifying principle and believes that he found it in the dynamic factors involved in infantile sexuality. Dr. Leach has given an insight into a number of cases of perversions. By contrast, I wish to report on a patient with multiple perversions who has been followed for the last fifteen years.

This man came to me because of difficulties in work. He was infantile and somewhat impulsive, stubborn and pouty. Whenever things did not go to his liking he would become angry, so that he was unable to adjust to customers or other salesmen. Generally he would withdraw into the basement and sit for hours apparently brooding, or, as he called it, "living in," while he indulged in a host of perverse fantasies. It was at first difficult to get him to talk about

them freely, but when once started he poured forth a flood of anal fantasies of the most diverse kinds. He repeated them innumerable times. Any attempt to stop him would be met with the protest: "Please, don't stop me! I must talk this out! I must get rid of this!" I gradually learned that all attempts at pressure or discipline were useless; that he would only become more upset and pester and hound me until things were once more on an even keel. Frequently he would project his anger on me and yell loudly. In the early years I was not always willing to stand for this; on occasions, when he became too violent, I put him out of the office. This procedure, however, I found unavailing, and gradually he taught me the analytic method of patient listening. Since then he has made progress somewhat more rapidly. He was sexually potent, but coitus was definitely masturbatory. He practiced some perversions with his wife, but the perverse fantasies were far richer. He dilated on them ad infinitum. He claimed to have seen his parents in coitus frequently, to have practiced cunnilingus on his mother, the maids and aunts. He stated that they had great trouble in training him to cleanliness, that he smeared and ate feces whenever possible. For this he was beaten regularly, but without avail. Generally, such an orgy of cophrophilia and coprophagia was followed by nausea and vomiting.

At the age of 4, when his brother was born, he was pushed out of the center of attention. He recalled that when relatives on a Sunday admired the baby he felt neglected. He knew, however, a sure way of drawing attention to himself. He went into the toilet, passed a stool, returned triumphantly holding aloft a fecal mass and said: "Look, mamma, look!" And, sure enough, they all looked! He claimed that they all beat him in turn. For a long time he used to talk about the "three C's," the vernacular for the vagina, the penis and the outhouse. He rolled these words with every evidence of relish. He liked not only to say them, but to hear them. Once he took a trip on a small steamer up a narrow river, with farms and outhouses on both banks. He had the most wonderful time picturing himself diving in and out of the outhouses! The outhouse to him was also a symbol of the uterus. In the early days he had many fantasies of anal birth and anal coitus. Later, these became transferred to the uterus and the vagina.

He continually had trouble with the doorman, his employer and other salesmen. The doorman was either the kindly father, who fed him and whom he liked as long as he was in favor, or the hated father, who preferred the other siblings to him. Then he would set to work to get rid of him, often ingeniously, usually for a double reason. He would say: "I love him too much, and I have got to get rid of him in order to free myself of him. Furthermore, I must get rid of him because he is unfair. He feeds some of the other boys." He would watch for irregularities and report them to the owner, who was an old friend of his father. In this way he managed to have four doormen discharged. The owner of the store was "the big father." About him he had many fantasies; for example, the store was in his abdomen and everybody passed in and out of his anus; the pipes were tapeworms. Other fantasies concerned his mother leaving the father, working in houses of prostitution and his watching all kinds of actions and perversions. The most bizarre fantasy concerned his father. In 1902, when the family lived in Chicago among Negroes, the patient stated that one evening a Negress deposited a child in their house, saying that it belonged to the patient's father. This caused great upset between the parents. The patient was jealous of the Negro brother; he tried to circumcise him with a razor, but cut off the penis and the child bled to death. When the parents returned the father was frantic. He cut up the child and tried to burn the pieces in the furnace, only to discover that it made too much stench. So he placed the remains in a gunny sack, rowed out on Lake Michigan and dropped them in the water. The blood-stained boat and the absence of the baby were discovered; the Negro people became threatening, and for protection the family was placed in custody in Evanston. He claimed that race riots resulted and that the trial was a famous one, with headlines in all the papers of the country. He was so sure of the accuracy of this fantasy that he only

smiled at me when I asked him to go to the library and look up the newspapers under the dates that he had given. He was crestfallen when he had to admit that he was not able to find any mention of what had seemed to him so real. More recently, he has worked through the material and has become aware that this fantasy was a distortion of his desire to castrate and eliminate his rival, the brother.

In the last several years I have treated him more analytically. He was made aware of the constant repetition through the preceding years. Gradually he lost the intense enjoyment in anal material and passed to cunnilingus and fellatio. During the last six months he has been more on a genital level. He bought a cocker spaniel; he was much interested in worming him and bathing him, and was fascinated by the size and color of the penis and testes. He had previously had a female dog which had been spayed. Suddenly an obsessive idea came to him that he would have to castrate this dog; that his former employer, the friend of his father, had advised him to have the other dog spayed and that the command held for this dog also. He realized this as an obsessive and "crazy" idea, but had great difficulty in restraining himself. It was conjectured that he considered the dog a sibling rival and that he wished to castrate him as he had in fantasy castrated his brother. From this material it was not hard to lead him back to masturbation, particularly infantile masturbation. A whole flood of memories came through then—how he had played with himself, and how his mother and father had threatened to cut his "ninny" off. He had neatly turned the threats of punishment to his own uses. He went everywhere taking out his penis and imitating the action of scissors or shears with his fingers. Touching the penis, he would say: "Papa and mamma threaten to cut my 'ninny' off because I am a bad boy, because I am a bad boy." At first he claimed that everybody spanked him and threatened to castrate him. More recently, he stated that it was mainly the father.

In this case, particularly, I have gained considerable understanding through the analytic approach. Though the patient has made marked strides and has achieved definite improvement and a far better adjustment to reality than before, there is still much to be accomplished, for he sees me only once or twice a week.

I believe that the relatively small number of perverts who fight against their difficulties and wish to discard them because they are in conflict with their ideals and social adjustments can be benefited if use is made of analytic understanding and technic. Also, patients with perversions which are combined with neuroses are more likely to come to the psychiatrist or the analyst for treatment. The majority of perverts are not amenable to treatment because they do not seek the physician, for the reason that the pleasure gain is too great. In cases in which the perversion is forced into the open because of difficulty with the law, the patients generally discontinue consultation as soon as the pressure from that source ceases.

With respect to perversions in general, it seems at first glance as if they are merely a continuation of an infantile partial instinctive sexual gratification. However, analysis of cases of this type has revealed that this is not so, that the sexual psychopathic person passes into the oedipus phase and regresses from that level to an earlier one which gave intense instinctual gratification. In other words, the general repression following the oedipus situation was more or less successful but could not engulf the highly pleasurably toned partial instinct, and the ego therefore had to accept it and make a full or unwilling adjustment to it. Here the perversion displaces the primacy of the genital instinct. With less adequate repression, other partial instincts also break through and are dealt with by neurotic compromises. The pervert has preserved a particular part of his infantile sexuality, but this is only like the peak of the iceberg projecting above the water. All other forms of infantile activity are repressed. One cannot say whether the intensity of the partial instinct is due to constitutional factors or to conditioning and environmental influences.

In the case of neuroses the infantile fantasies break through the barriers of repression, but only by making a compromise with the repressing forces in forming an alien and hostile neurotic symptom. In the case of perversion, however, the particular infantile sexual activity is more or less acceptable to the ego and is pleasurably toned. Satisfaction in perversion, whether obtained through action or fantasy, can then be equated with the neurotic symptom. Except for the pleasure gained in the case of perversion, the two have much in common. They are resultants of infantile sexual life, which on the whole has been repressed. They are really comparatively small residues of a great developmental process. They are representatives of unconscious drives and instinctual vicissitudes appearing in consciousness. Both are only exaggerations of processes which occur in normal mental development.

Surgical Treatment of Dystonia, Paralysis Agitans and Athetosis. Dr. Roland M. Klemme, St. Louis.

All methods of attack in the chemical treatment of paralysis agitans and athetosis have, up to the present, given discouraging results. Various drugs have given only short-lived relief, and there has been full knowledge that a permanent satisfactory result is outside the realm of this type of treatment. Many therapeutic agents have been used, some supposedly based on physiologic action and others purely empiric. Because of constant failure from the use of chemotherapy, dystonia has been attacked from the surgical point of view.

The work reported was based on Wilson's theory, published in 1912, in which he emphasized the part played by afferent impulses and said that choreic movements are due to lesions in the afferent pathway from the cerebellum by way of the cerebellar peduncle to the midbrain and thence to the thalamus, from which there is a widespread radiation to the frontal and parietal lobes of the brain; the latter cortical areas suffer impairment of transcortical inhibition, and voluntary movement patterns are displaced by involuntary choreic ones. It seems logical to conclude, therefore, that a defect in transcortical inhibition may produce the tremor and spasticity seen in this type of disease.

With this evidence at hand, premotor cortical excisions were carried out in over 100 patients. The results are amazing. The operative risk is about 10 per cent. A word picture of the conditions before and after operation is almost impossible to give. It suffices that these patients are rehabilitated and can carry on their former work after operative intervention. In other words, they have been made an economic asset instead of a liability. The first procedure was carried out in January 1937. To date there has been no recurrence.

Book Reviews

Injuries of the Skull, Brain and Spinal Cord: Neuro-Psychiatric, Surgical and Medico-Legal Aspects. Edited by Samuel Brock. Price, $7. Pp. 632, with 63 illustrations. Baltimore: Williams and Wilkins Company, 1940.

This symposium, by 22 well known contributors from the United States, Canada and Great Britain, represents a valuable summary of present day knowledge of the neurologic, psychiatric, surgical and medicolegal aspects of injury of the central nervous system. Although containing little that is not common neurologic and psychiatric knowledge, the 22 chapters cover the subject exhaustively. As between the individual contributions, there are only slight overlapping and remarkably little divergence of opinion. Even a critical reader will find only a few unreliable statements or inaccuracies and little speculation. (On page 8 it is erroneously stated that blood typing is unnecessary when children are given transfusion of blood from their parents). On the whole, the work represents a fair, complete and up-to-date compilation of fact. The format is attractive, and a complete index enhances the value of the book.

These things said, certain comments and criticisms must be added. Viewed as a whole, the work reflects certain gaps which exist in the knowledge and understanding of injuries of the central nervous system. The concept of concussion is, for example, still vague and controversial. The word has different meanings for the clinician and the pathologist, and speculation as to its pathologic nature seems futile until more data are available. Efforts by the editor to reconcile discrepancies by means of numerous footnotes fail to eliminate the confusion. Again, the possible role played by trauma in producing such neurologic conditions as convulsions, tumor of the brain, amyotrophic lateral sclerosis and paralysis agitans remains controversial in respectively varying degrees. Likewise, the importance of birth trauma as a factor in the various spastic conditions of childhood is still uncertain, although probably not as great as is sometimes thought. Controversial questions regarding the immediate treatment of serious craniocerebral injuries are inadequately discussed, although an outline is given which will probably meet with fairly general approval.

This book is by far the best now available in English on the subject. It will prove useful to student, industrial physician and neurologist. Although somewhat technical for use by the legal profession, it nevertheless brings for them within brief compass authoritative information otherwise scattered widely in a contradictory and frequently unreliable periodical "literature." Even so, the wise attorney will avoid taking sentences and paragraphs out of their context and will remember that controversy exists about many questions treated here somewhat dogmatically.

The poorest portion of the book is the chapter on malingering. Despite introductory paragraphs which seem to indicate that the author understands the difference between wilful and unconscious simulation of illness, this chapter is little more than a catalogue of "tricks" for uncovering deception, which may as easily be unconscious as wilful. The difference between malingering and hysteria is generally accepted as real, but practically malingering is proved only with the greatest difficulty, if at all. The author seems to be unaware of the philosophic subtlety of the distinction, and consequently makes many statements which may cause great misunderstanding and confusion in the courtroom and result in injustice to many patients. On the other hand, the same author's chapter, summarizing legal information for medical readers, with which the book closes, makes interesting reading and should prove valuable.

Die Pathologie der optischen Nachbilder und ihre klinische Verwertung. By V. Vujic and K. Levi. Pp. 86. New York: S. Karger.

Vujic and Levi point out that although after-images have been extensively investigated by physiologists and psychologists, their pathology is unknown. They can be studied by simple methods. The patient fixes on an illuminated colored glass plate for thirty seconds; then the illumination of this glass plate is turned off and the patient is requested to look at a dull white background. After a latent period of from four to ten seconds the after-image appears, which has the same color (positive image) or the complementary color (negative after-image); this lasts for from eight to sixty seconds. The clinical importance of this method of examination lies in the fact that disturbances in the appearance of the after-image precede the disturbances of color vision and of the visual fields in diseases of the central nervous system, such as tabes, multiple sclerosis and tumor of the brain. In cases of genuine, as well as of traumatic, epilepsy absence of the optic after-image was found for one or several colors. Such a disturbance may help in the differential diagnosis of neurosis and organic lesion and in the determination of the injured hemisphere. This important monograph, which is based on 498 cases, should be of interest to every one working in neuro-ophthalmology.

The Public Health Nurse and Her Patient. By Ruth Gilbert, R.N. Price, $2.25. Pp. 396, including index. New York: The Commonwealth Fund, 1940.

The author, well prepared by training and experience both as a public health nurse and as a psychiatric social worker, has made through this interesting book an important contribution. The book not only is of value to the public health nurse but should appeal strongly to all nurses for its emphasis on the part played in disease by the habitual emotional reactions of the patient. The fact that an illness cannot be an isolated incident in the life of the patient must be of significance to all concerned with the intelligent care of the sick. Noteworthy are the topics which deal with the building up of right relationships between nurse and patient, particularly with reference to the need of recognition of individual differences; the relationships with co-workers and allied groups, and the importance of the achievement of skill in conference technics. Writing from the point of view of mental hygiene, the author has skilfully interwoven throughout the book principles of mental hygiene together with many apt and pertinent illustrations from actual experiences in the field.

Psychiatric Nursing Technic. By A. E. Bennett, M.D., and Avis B. Purdy, R.N. Pp. 172, including index. Philadelphia: F. A. Davis Company, 1940.

This is the first book to deal specifically with the clearly defined technics established through the development of modern psychiatric medicine. In the words of the authors, the book is concerned with practical psychiatric treatment procedures, rather than with psychiatric nursing or treatment. It is intended to serve as a guide to nurses and attendants. Emphasis is placed throughout on the practical rather than the theoretic point of view. While the book has much to recommend it for use by the attendant as well as by students of nursing, it would seem that much of the material presumes a knowledge of basic principles of nursing beyond that of the average attendant. The convenient arrangement of the material makes the book a valuable reference and should make a real contribution toward improvement in care of the psychiatric patient.